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J Gen Virol. 2004 Sep;85(Pt 9):2603-13.
PMID: 15302954 [PubMed - in process]

☐ 2: Billick E, Seibert C, Pugach P, Ketas T, Trkola A, Endres MJ, Murgolo NJ, Coates E, Reyes GR, Baroudy BM, Sakmar TP, Moore JP, Kuhmann SE. Related Articles, Links

☐ The differential sensitivity of human and rhesus macaque CCR5 to small-molecule inhibitors of human immunodeficiency virus type 1 entry is explained by a single amino acid difference and suggests a mechanism of action for these inhibitors.
J Virol. 2004 Apr;78(8):4134-44.
PMID: 15047829 [PubMed - indexed for MEDLINE]

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☐ 3: Liu Y, Liu H, Kim BO, Gattone VH, Li J, Nath A, Blum J, He JJ. Related Articles, Links


☐ CD4-independent infection of astrocytes by human immunodeficiency virus type 1: requirement for the human mannose receptor.
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☐ 4: Peters B, Whittall T, Babaahmady K, Gray K, Vaughan R, Lehner T. Related Articles, Links


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Lancet. 2004 Feb 14;363(9408):518-24.
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☐ 5: Biorn AC, Cocklin S, Madani N, Si Z, Ivanovic T, Samanen J, Van Ryk DI, Pantophlet R, Burton DR, Freire E, Sodroski J, Chaiken IM. Related Articles, Links


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J Infect Dis. 2004 Feb 15;189(4):624-33. Epub 2004 Feb 04.
PMID: 14767815 [PubMed - indexed for MEDLINE]


Related Articles, Links
-  **7:** Schaeffer E, Soros VB, Greene WC.


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-  **8:** Nabatov AA, Pollakis G, Linnemann T, Kliphuis A, Chalaby MI, Paxton WA.


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 Inhibition of chemokine receptor function by membrane cholesterol oxidation.
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
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Blood. 2004 Feb 15;103(4):1211-7. Epub 2003 Oct 23.
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- ☐ **17:** [Kumar S, Kwei GY, Poon GK, Iliff SA, Wang Y, Chen Q, Franklin RB, Didolkar V, Wang RW, Yamazaki M, Chiu SH, Lin JH, Pearson PG, Baillie TA.](#) [Related Articles, Links](#)
 Pharmacokinetics and interactions of a novel antagonist of chemokine receptor 5 (CCR5) with ritonavir in rats and monkeys: role of CYP3A and P-glycoprotein.
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- ☐ **18:** [Amara A, Vidy A, Boulla G, Mollier K, Garcia-Perez J, Alcamí J, Blanpain C, Parmentier M, Virelizier JL, Charneau P, Arenzana-Seisdedos F.](#) [Related Articles, Links](#)
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 Two mechanisms for human immunodeficiency virus type 1 inhibition by N-terminal modifications of RANTES.
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- ☐ **20:** [Verani A, Lusso P.](#) [Related Articles, Links](#)
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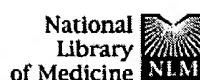
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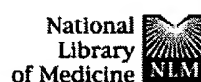
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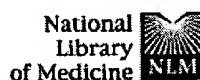
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#1	Search Derdeyn C	09:26:49	78

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TITLE: Fluorescence resonance energy transfer screening assay
for the identification of compounds that are capable
of abrogating macrophage-tropic HIV-1 cell fusion

INVENTOR(S): Allaway, Graham P.; Litwin, Virginia M.; Maddon, Paul
J.

PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., USA

SOURCE: U.S., 21 pp., Cont.-in-part of U.S. Ser. No. 475,515.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

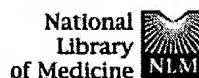
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PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6261763	B1	20010717	US 1998-973601	19980316
WO 9641020	A1	19961219	WO 1996-US9894	19960607
W: AU, CA, JP, MX, US				
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US 2003044770	A1	20030306	US 1999-412284	19991005
US 2002045161	A1	20020418	US 2001-904356	20010712
PRIORITY APPLN. INFO.:			US 1995-475515	A2 19950607
			WO 1996-US9894	W 19960607
			US 1998-973601	A1 19980316

ABSTRACT:

Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this application was to develop a novel screening assay to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory-adapted strain. To this end, a novel **fusion assay** was developed on the basis of the principle of resonance energy transfer, using **HeLa** cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1LAI or the macrophage-tropic primary isolate HIV-1JR-FL. These cells fused with CD4+target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, **HeLa** cells expressing HIV-1JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1JR-FL and HIV-1LAI in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. The claimed invention will facilitate the screening and identification of novel agents that are capable of inhibiting these interactions.



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=> L1 and hos
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    3571 HOSES
    4222 HOS
        (HOS OR HOSES)
L6      2 L1 AND HOS

=> L1 and Hela
    28407 HELA
    19 HELAS
    28425 HELA
        (HELA OR HELAS)
L7      19 L1 AND HELA

=> tat and L7
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    49 TATS
    6661 TAT
        (TAT OR TATS)
L8      3 TAT AND L7

=> LTR and L7
    5531 LTR
    910 LTRS
    5719 LTR
        (LTR OR LTRS)
L9      5 LTR AND L7

=> CCR5 and L1
    3032 CCR5
L10     37 CCR5 AND L1

=> CD4 and L10
    42047 CD4
L11     23 CD4 AND L10

=> reporter and L11
    37947 REPORTER
    1288 REPORTERS
    38645 REPORTER
        (REPORTER OR REPORTERS)
L12     5 REPORTER AND L11

=> LTR and L11
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    5719 LTR
        (LTR OR LTRS)
L13     1 LTR AND L11

=> DIS L13 1 IBIB IABS

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=> fusion (w) assay
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    8695 FUSIONS
    235583 FUSION
        (FUSION OR FUSIONS)
    309256 ASSAY
    132668 ASSAYS
    404564 ASSAY
        (ASSAY OR ASSAYS)
L1      391 FUSION (W) ASSAY

=> Hos (w) CD4
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    3571 HOSES
    4222 HOS
        (HOS OR HOSES)
    42047 CD4
L2      35 HOS (W) CD4

=> L1 and L2
L3      1 L1 AND L2

=> L1 and CCR5
    3032 CCR5
L4      37 L1 AND CCR5

=> inhibitor and L4
    448362 INHIBITOR
    467669 INHIBITORS
    721466 INHIBITOR
        (INHIBITOR OR INHIBITORS)
L5      7 INHIBITOR AND L4

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ACCESSION NUMBER: 2001:618156 CAPLUS
 DOCUMENT NUMBER: 135:191251
 TITLE: Cell **fusion assays** using
 fluorescence resonance energy transfer
 INVENTOR(S): Sullivan, Kathleen A.; Benincasa, Diana; Cascieri,
 Margaret A.; Mitnaul, Lyndon J.; Shiao, Lin-Lin; Tota,
 Michael R.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 59 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003523204	T2	20030805	JP 2001-560366	20010213
US 2003036108	A1	20030220	US 2002-204200	20020816
PRIORITY APPLN. INFO.:			US 2000-183309P	P 20000217
			WO 2001-US4677	W 20010213

ABSTRACT:

Methods of identifying **inhibitors** of the fusion of two types of cells, particularly when fusion is mediated by the interaction of a viral protein and such cellular proteins as CD4 and chemokine receptors, are disclosed. The present invention is directed to methods of identifying *****inhibitors***** of the fusion of two types of cells, one of which contains the enzyme β -lactamase and the other of which contains a fluorescent substrate of β -lactamase. The substrate is a compound comprising two moieties that are connected by a linker that is susceptible to cleavage by β -lactamase. Each moiety is independently fluorescent and the emission spectrum of one moiety overlaps the absorption spectrum of the other moiety. The mol. configuration of the substrate is such that, when the linker is intact, fluorescence resonance energy transfer (FRET) can occur between the two fluorescent moieties. When the linker has been cleaved by β -lactamase, the two moieties are no longer phys. linked and can thus diffuse apart. This results in FRET being either abolished or greatly diminished. After fusion, when the two cytoplasms have mixed, β -lactamase from one cell will cleave the substrate from the other cell, diminishing or abolishing FRET. Thus, the measurement of FRET can serve as a measure of the amount of fusion that has occurred between the two types of cells. The method is used to identify *****inhibitors***** of fusion mediated by an HIV-1 Env protein in the cytoplasmic membrane of one cell and CD4 and a chemokine receptor in the cytoplasmic membrane of the other cell. The two cells serve as models for the fusion process that occurs during HIV-1 infection. The **inhibitors** identified using the present invention are expected to be useful as drugs to prevent or ameliorate the effects of HIV-1 infection and AIDS.

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:455171 CAPLUS

DOCUMENT NUMBER: 139:67648

TITLE: Human immunodeficiency virus type 1 entry
inhibitors selected on living cells from a
library of phage chemokines

AUTHOR(S): Hartley, Oliver; Dorgham, Karim; Perez-Bercoff,
Danielle; Cerini, Fabrice; Heimann, Anouk; Gaertner,
Hubert; Offord, Robin E.; Pancino, Gianfranco; Debre,
Patrice; Gorochov, Guy

CORPORATE SOURCE: Immunologie A., CERVI, INSERM U543, Hospital
Pitie-Salpetriere, Paris, Fr.

SOURCE: Journal of Virology (2003), 77(12), 6637-6644
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The chemokine receptors **CCR5** and **CXCR4** are promising non-virus-encoded targets for human immuno-deficiency virus (HIV) therapy. We describe a selection procedure to isolate mutant forms of RANTES (CCL5) with antiviral activity considerably in excess of that of the native chemokine. The phage-displayed library of randomly mutated and N-terminally extended variants was screened by using live **CCR5**-expressing cells, and two of the selected mutants, P1 and P2, were further characterized. Both were significantly more potent HIV **inhibitors** than RANTES, with P2 being the most active (50% inhibitory concentration of 600 pM in a viral coat-mediated cell

fusion assay, complete protection of target cells against primary HIV type 1 strains at a concentration of 10 nM). P2 resembles AOP-RANTES in that it is a superagonist of **CCR5** and potently induces receptor sequestration. P1, while less potent than P2, has the advantage of significantly reduced signaling activity via **CCR5** (30% of that of RANTES). Addnl., both P1 and P2 exhibit not only significantly increased affinity for **CCR5** but also enhanced receptor selectivity, retaining only trace levels of signaling activity via CCR1 and CCR3. The phage chemokine approach that was successfully applied here could be adapted to other chemokine-chemokine receptor systems and used to further improve the first-generation mutants reported in this paper.

ACCESSION NUMBER: 2003:900264 CAPLUS
DOCUMENT NUMBER: 140:92158
TITLE: Establishment of an HIV cell-cell **fusion assay** by using two genetically modified HeLa cell lines and **reporter** gene
AUTHOR(S): Sakamoto, Tatsunori; Ushijima, Hiroshi; Okitsu, Shoko; Suzuki, Eiko; Sakai, Koji; Morikawa, Shigeru; Muller, Werner E. G.
CORPORATE SOURCE: Graduate School of Medicine, Department of Developmental Medical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan
SOURCE: Journal of Virological Methods (2003), 114(2), 159-166
CODEN: JVMEHD; ISSN: 0166-0934
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

ABSTRACT:

Infection of human cells with the human immunodeficiency virus type I (HIV-1) can be mimicked by a fusion process between cells expressing the HIV envelope protein (Env) and cells expressing both human **CD4** together with the appropriate human chemokine receptors. In this study, a T-tropic HIV cell-cell **fusion assay** was established that utilized **CD4**, human CXCR4 and HIV NL4-3 gp160 as fusion components and a T7 polymerase-activated luciferase as a **reporter** system. The HeLa T4 cells used, expressed **CD4** and CXCR4, and the applied HeLa KS386 cells expressed HIV NL4-3 gp160. By combining HeLa T4 cells with HeLa KS386 cells, an approx. about 100- to 300-fold increase in luciferase activity could be elicited relative to the control. The addition of anti-**CD4** monoclonal antibody (Mab) (RPA-T4) or anti-CXCR4 Mab (12G5) in the assay significantly inhibited the fusion event; in contrast, an anti-**CCR5** Mab (2D7) had no effect, indicating that the **fusion assay** was **CD4** and CXCR4 dependent. In this report, fusion events could be monitored by both the luciferase **reporter** system and syncytia formation. Fusion events were monitored and compared using these two approaches. The luciferase **reporter** system was found to be more sensitive than syncytia formation. Moreover, compared with previous HIV fusion models, such as using recombinant vaccinia viruses, this system has several advantages, including simplicity and sensitivity. Finally, the system provides a powerful tool to study fusion mechanisms mediated by T-tropic HIV gp160, as well as to screen for fusion-blocking antibodies and antiviral agents.

L12 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:731875 CAPLUS

DOCUMENT NUMBER: 140:138613

TITLE: Development of a novel high-throughput surrogate assay to measure HIV envelope/**CCR5/CD4**-mediated viral/cell fusion using BacMam baculovirus technology

AUTHOR(S): Jenkinson, Stephen; McCoy, David C.; Kerner, Sandy A.; Ferris, Robert G.; Lawrence, Wendell K.; Clay, William C.; Condreay, J. Patrick; Smith, Chari D.

CORPORATE SOURCE: GlaxoSmithKline Research and Development, Research Triangle Park, NC, USA

SOURCE: Journal of Biomolecular Screening (2003), 8(4), 463-470

CODEN: JBISF3; ISSN: 1087-0571

PUBLISHER: Sage Publications

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The initial event by which M-tropic HIV strains gain access to cells is via interaction of the viral envelope protein gp120 with the host cell **CCR5** co-receptor and **CD4**. Inhibition of this event reduces viral fusion and entry into cells in vitro. The authors have employed BacMam baculovirus-mediated gene transduction to develop a cell/cell **fusion assay** that mimics the HIV viral/cell fusion process and allows high-throughput quantification of this fusion event. The assay design uses human osteosarcoma (HOS) cells stably transfected with cDNAs expressing **CCR5**, **CD4**, and long terminal repeat (LTR)-luciferase as the recipient host cell. An HEK-293 cell line transduced with BacMam viral constructs to express the viral proteins gp120, gp41, tat, and rev represents the virus. Interaction of gp120 with **CCR5/CD4** results in the fusion of the 2 cells and transfer of tat to the HOS cell cytosol; tat, in turn, binds to the LTR region on the luciferase **reporter** and activates transcription, resulting in an increase in cellular luciferase activity. In conclusion, the cell/cell **fusion assay** developed has been demonstrated to be a robust and reproducible high-throughput surrogate assay that can be used to assess the effects of compds. on gp120/**CCR5** /**CD4**-mediated viral fusion into host cells.

ACCESSION NUMBER: 2000:30063 CAPLUS
DOCUMENT NUMBER: 132:345932
TITLE: New reporter cell lines to study macrophage-tropic HIV envelope protein-mediated cell-cell fusion
AUTHOR(S): Hong, Yu-Long; Wu, Lan-Hsin; Cui, Mei; McMaster, Gary; Hunt, Stephen W., III; Chung, Fu-Zon
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Division of the Warner-Lambert Company, Ann Arbor, MI, 48105, USA
SOURCE: AIDS Research and Human Retroviruses (1999), 15(18), 1667-1672
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

ABSTRACT:

The infection of human cells by HIV-1 virus can be mimicked by a fusion process between cells expressing the HIV envelope protein (Env) and cells expressing both human **CD4** (huCD4) and appropriate human chemokine receptors. In this study, a macrophage-tropic (M-tropic) HIV cell-cell **fusion** *****assay***** was established that utilized huCD4, human **CCR5** (huCCR5), and HIV ADAgp160 as fusion components and a Gal4/VP16-activated luciferase as a reporter system. By combining CHO cells expressing huCD4 and huCCR5 with CHO cells expressing HIV ADAgp160, a 300-fold increase in luciferase activity could be elicited relative to control. No luciferase activity was detected when HXB2gp160 (T-tropic) was used instead of ADAgp160 (M-tropic) as the fusion partner in the assay. Addition of anti-huCD4 (RPA-T4) or anti-huCCR5 (2D7) monoclonal antibodies in the assay inhibited the fusion event; in contrast, an anti-CXCR4 (12G5) monoclonal antibody had little effect, indicating that the **fusion assay** was huCD4 and huCCR5 dependent. The cell-cell fusion occurred in a time-dependent manner; the maximum luciferase activity was detected about 8 h after mixing the cells. The fusion events could also be monitored by another reporter system in which Gal4/VP16 activated green fluorescent protein (GFP) was used as the reporter instead of luciferase. In combination with fluorescence microscopy, the GFP reporter system allowed visualization of the fusion events in real time. Compared with previously described HIV fusion models, this system has several advantages, including simplicity, sensitivity, and the ability to allow continuous monitoring of the HIV cell-cell fusion event. Finally, this cell-cell fusion system is easily adapted to study other HIV fusion events.

L11 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:651376 CAPLUS

DOCUMENT NUMBER: 131:335664

TITLE: **CCR5** HIV-1 coreceptor activity. Role of cooperativity between residues in N-terminal extracellular and intracellular domains

AUTHOR(S): Wang, Zixuan; Lee, Benhur; Murray, James L.; Bonneau, Fabien; Sun, Yi; Schweickart, Vicki; Zhang, Tianyuan; Peiper, Stephen C.

CORPORATE SOURCE: Henry Vogt Cancer Research Institute, University of Louisville, Louisville, KY, 40202, USA

SOURCE: Journal of Biological Chemistry (1999), 274(40), 28413-28419

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Human (H) **CCR5** is the primary coreceptor for ENV-mediated fusion by R5 strains of human immunodeficiency virus type 1, whereas mouse (M) **CCR5** lacks this function. An array of 23 H/M-**CCR5** hybrids containing increasing amts. of H-**CCR5** extending from the N terminus generated by random chimeraesis had a biphasic pattern of coreceptor activity with JRFL and 89.6, revealing active regions in the N-terminal extracellular domain (N-ED) and at the junction of cytoplasmic loop 3. The M-**CCR5** mutant in which divergent residues were replaced with the corresponding H-**CCR5** N-ED sequence (NyYTSE) gained coreceptor function in fusion but not infection expts. A M-**CCR5** double mutant with substitution of human sequences for divergent residues from the N-ED and cytoplasmic loop 3 had augmented coreceptor activity in **fusion** assays and gain of function in infection expts. The SIV-251 ENV utilized H- and M-**CCR5** and variants. Flow cytometric anal. of M-**CCR5** mutants and bifunctional receptors composed of **CD4** domains fused to M-**CCR5** mutants excluded the possibility that differences in coreceptor activity resulted from variations in cell surface expression. Thus, the coreceptor activity of the H-**CCR5** N-ED is modulated by intracellular residues, illustrating the complexity of **CCR5** requirements for interaction with ENV.

L11 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:379817 CAPLUS

DOCUMENT NUMBER: 131:183689

TITLE: Role of the HIV type 1 glycoprotein 120 V3 loop in determining coreceptor usage

AUTHOR(S): Verrier, Florence; Borman, Andrew M.; Brand, Denys; Girard, Marc

CORPORATE SOURCE: Unite de Virologie Moleculaire (CNRS URA 1966),
Departement de Virologie, Institut Pasteur, Paris,
75724, Fr.

SOURCE: AIDS Research and Human Retroviruses (1999), 15(8),
731-743

CODEN: ARHRE7; ISSN: 0889-2229

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Macrophage (M)-tropic HIV-1 isolates use the β -chemokine receptor ***CCR5*** as a coreceptor for entry, while T cell line-adapted (TCLA) strains use CXCR4 and dual-tropic strains can use either CCR5 or CXCR4. To investigate the viral determinants involved in choice of coreceptor, we used a **fusion assay** based on the infection of ***CD4*** + HeLa cells that express one or both coreceptors with Semliki Forest virus (SFV) recombinants expressing the native HIV-1 gp160 of a primary M-tropic isolate (HIV-1BX08), a TCLA isolate (HIV-1LAI), or a dual-tropic strain (HIV-1MN). We examined whether the V3 region of these glycoproteins interacts directly with the corresponding coreceptors by assaying coreceptor-dependent cell-to-cell fusion mediated by the different recombinants in the presence of various synthetic linear peptides. Synthetic peptides corresponding to different V3 loop sequences blocked syncytium formation in a coreceptor-specific manner. Synthetic V2 peptides were also inhibitory for syncytium formation, but showed no apparent coreceptor specificity. A BX08 V3 peptide with a D320 \rightarrow R substitution retained no inhibitory capacity for BX08 Env-mediated cell-to-cell fusion, but inhibited LAI Env-mediated fusion as efficiently as the homologous LAI V3 peptide. The same mutation engineered in the BX08 env gene rendered it able to form syncytia on **CD4+CXCR4+** ***CCR5*** - HeLa cells and susceptible to inhibition by SDF-1 α and MIP-1 β . Other substitutions tested (D320 \rightarrow Q/D324 \rightarrow N or S306 \rightarrow R) exhibited intermediate effects on coreceptor usage. These results underscore the importance of the V3 loop in modulating coreceptor choice and show that single amino acid modifications in V3 can dramatically modify coreceptor usage. Moreover, they provide evidence that linear V3 loop peptides can compete with intact cell surface-expressed gp120/gp41 fo

L11 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:115164 CAPLUS

DOCUMENT NUMBER: 128:216242

TITLE: Identification of determinants on a dualtropic human immunodeficiency virus type 1 envelope glycoprotein that confer usage of CXCR4

AUTHOR(S): Cho, Michael W.; Lee, Myung K.; Carney, Michelle C.; Berson, Joanne F.; Doms, Robert W.; Martin, Malcolm A.

CORPORATE SOURCE: Lab. of Mol. Microbiol., Natl. Inst. of Allergy and Infect. Dis., Natl. Inst. of Health, Bethesda, MD, 20892-0460, USA

SOURCE: Journal of Virology (1998), 72(3), 2509-2515

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The chemokine receptors **CCR5** and **CXCR4**, in combination with *****CD4*****, mediate cellular entry of macrophage-tropic (M-tropic) and T-cell-tropic strains of human immunodeficiency virus type 1 (HIV-1), resp., while dualtropic viruses can use either receptor. The authors have constructed a panel of chimeric viruses and envelope glycoproteins in which various domains of the dualtropic HIV-1DH12 gp160 were introduced into the genetic background of an M-tropic HIV-1 isolate, HIV-1AD8. These constructs were employed in cell fusion and virus infectivity assays using peripheral blood mononuclear cells, MT4 T cells, primary monocyte-derived macrophages, or HOS-**CD4** cell lines, expressing various chemokine receptors, to assess the contributions of different gp120 subdomains in coreceptor usage and cellular tropism. As expected, the dualtropic HIV-1DH12 gp120 utilized either **CCR3**, **CCR5**, or **CXCR4**, whereas HIV-1AD8 gp120 was able to use only **CCR3** or **CCR5**. The authors found that either the V1/V2 or the V3 region of HIV-1DH12 gp120 individually conferred on HIV-1AD8 the ability to use **CXCR4**, while the combination of both the V1/V2 and V3 regions increased the efficiency of **CXCR4** use. In addition, while the V4 or the V5 region of HIV-1DH12 gp120 failed to confer the capacity to utilize **CXCR4** on HIV-1AD8, these regions were required in conjunction with regions V1 to V3 of HIV-1DH12 gp120 for efficient utilization of **CXCR4**. Comparison of virus infectivity analyses with various cell types and cell **fusion assays** revealed assay-dependent discrepancies and indicated that events occurring at the cell surface during infection are complex and cannot always be predicted by any one assay.

L11 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:689214 CAPLUS

DOCUMENT NUMBER: 127:357970

TITLE: Promiscuous use of CC and CXC chemokine receptors in cell-to-cell fusion mediated by a human immunodeficiency virus type 2 envelope protein

AUTHOR(S): Bron, Romke; Klasse, P. J.; Wilkinson, David; Clapham, Paul R.; Pelchen-Matthews, Annegret; Power, Christine; Wells, Timothy N. C.; Kim, Jin; Peiper, Stephen C.; Hoxie, James A.; Marsh, Mark

CORPORATE SOURCE: MRC Laboratory for Molecular Cell Biology and Department of Biochemistry, University College London, London, WC1E 6BT, UK

SOURCE: Journal of Virology (1997), 71(11), 8405-8415

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The CC chemokine receptors CCR5, CCR2, and CCR3 and the CXC chemokine receptor CXCR4 have been implicated as CD4-associated cofactors in the entry of primary and cell line-adapted human immunodeficiency virus type 1 (HIV-1) strains. CXCR4 is also a receptor for T-cell-line-adapted, CD4-independent strains of HIV-2. With the exception of this latter example, little has been reported on the entry cofactors used by HIV-2 strains. Here the authors show that a CD4-dependent, T-cell-line-adapted HIV-2 strain uses CXCR4 and, to a lesser extent, CCR3 for fusion with and infectious entry into cells. In a cell-to-cell **fusion assay**, the envelope protein of this virus can utilize a wider repertoire of chemokine receptors to induce fusion. These include CCR1, CCR2, CCR3, CCR4, CCR5, CXCR2, and CXCR4. Kinetic anal. indicated that cell lines expressing the receptors that support infection, CXCR4 and CCR3, form syncytia more rapidly than do cell lines expressing the other receptors. Nevertheless, although less efficient, fusion with CXCR2 expressing cells was specific, since it was inhibited by antibodies against CXCR2. The extensive use of chemokine receptors in cell-to-cell fusion has implications for understanding the mol. basis of CD4-chemokine receptor-induced lentivirus fusion and may have relevance for syncytium formation and the direct cell-to-cell transfer of virus in vivo.

L9 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:204015 CAPLUS

DOCUMENT NUMBER: 129:80

TITLE: A simple assay system for examination of the inhibitory potential in vivo of decoy RNAs, ribozymes and other drugs by measuring the Tat-mediated transcription of a fusion gene composed of the long terminal repeat of HIV-1 and a gene for luciferase

AUTHOR(S): Koseki, Shiori; Ohkawa, Jun; Yamamoto, Rika; Takebe, Yutaka; Taira, Kazunari

CORPORATE SOURCE: MITI, National Institute of Bioscience and Human Technology, 1-1 Higashi, Tsukuba Science City, 305, Japan

SOURCE: Journal of Controlled Release (1998), 53(1-3), 159-173
CODEN: JCREEC; ISSN: 0168-3659

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Nucleic acid-based drugs, including antisense RNA and DNA, ribozymes and decoys appear to have potential for the suppression of the expression of specific genes. To allow the examination of the potential of such agents in vivo as anti-HIV drugs in standard labs., where facilities for handling live virions are not available, we constructed a simple assay system (HIV-1 model) that allows measurement of the extent of inhibition of Tat-mediated transcription of HIV-1 by nucleic acid-based drugs and other agents. In cells that harbor a stable chimeric long terminal repeat (LTR)-Luc construct (a fusion gene consisting of the LTR of HIV-1 and the gene for luciferase), total luciferase activity in an aliquot of cell lysate is dose- and promoter-dependent on transfection with a Tat expression plasmid, reflecting the character of the LTR promoter of HIV. When HeLa cells were co-transfected with the Tat expression plasmid and another plasmid that encoded the U6 promoter or the promoter of the gene for tRNA^{Val} linked to the trans-activating response (TAR) sequence, total luciferase activity was inhibited by 60 or 40%, resp. The inhibition was also dependent on the dose of the TAR expression plasmid. These results demonstrate the usefulness of this simple assay system for detection of the efficacy of a decoy RNA or a ribozyme in vivo, without a requirement for HIV-infected cells, by measurement of luciferase activity in vitro.

L9 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:438785 CAPLUS

DOCUMENT NUMBER: 125:136768

TITLE: Expression of HIV env gene in a human T cell line for a rapid and quantifiable cell fusion assay

AUTHOR(S): Moir, Susan; Poulin, Louise

CORPORATE SOURCE: Faculty Medicine, Laval University, Ste-Foy, QC, G1V 4G2, Can.

SOURCE: AIDS Research and Human Retroviruses (1996), 12(9), 811-820

CODEN: ARHRE7; ISSN: 0889-2229

PUBLISHER: Liebert

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins present at the surface of infected cells are known to mediate fusion with CD4-pos. target cells. In this study we have developed a novel Env-expressing cell line for investigating the fusion process in a biol. significant system. Cell surface expression of the HIV-1 env gene, isolated from the highly fusogenic strain SF33, was obtained in the CD4-neg. T cell line A2.01. To render the system versatile and efficient, HIV-1 regulatory proteins Tat and Rev were supplied in trans. The presence of Env at the cell surface was shown by cytofluorometry and immunofluorescence and precursor processing of gp160 to gp120/gp41 was demonstrated by Western blot. The fusion capacity of A2.01-Env cells was assessed by coculture with CD4-pos. T lymphocytes or the fusion indicator cell line, **HeLa-CD4-LTR- β -Gal**. By coinubation with CD4-pos. T cells such as SupT1, A2.01-Env cells were observed to mediate rapidly numerous well-defined syncytia in a reproducible fashion. By expressing Tat, they also had the capacity to trans-activate the **LTR-linked reporter β -Gal** gene following fusion with **HeLa-CD4-LTR- β -Gal** cells. The fusion-inhibiting anti-CD4 monoclonal antibodies Q425 and Q428 were used to block specifically Env-mediated fusion with CD4-pos. cells and to demonstrate application of this system to the search for potential fusion-blocking agents. Our system thus offers a biol. significant model for studying fusion events with the advantages of being rapid, reproducible, and versatile.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:438785 CAPLUS

DOCUMENT NUMBER: 125:136768

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AUTHOR(S): M~~oir~~, Susan; Poulin, Louise

CORPORATE SOURCE: Faculty Medicine, Laval University, Ste-Foy, QC, G1V 4G2, Can.

SOURCE: AIDS Research and Human Retroviruses (1996), 12(9), 811-820

CODEN: ARHRE7; ISSN: 0889-2229

PUBLISHER: Liebert

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins present at the surface of infected cells are known to mediate fusion with CD4-pos. target cells. In this study we have developed a novel Env-expressing cell line for investigating the fusion process in a biol. significant system. Cell surface expression of the HIV-1 env gene, isolated from the highly fusogenic strain SF33, was obtained in the CD4-neg. T cell line A2.01. To render the system versatile and efficient, HIV-1 regulatory proteins **Tat** and Rev were supplied in trans. The presence of Env at the cell surface was shown by cytofluorometry and immunofluorescence and precursor processing of gp160 to gp120/gp41 was demonstrated by Western blot. The fusion capacity of A2.01-Env cells was assessed by coculture with CD4-pos. T lymphocytes or the fusion indicator cell line, **HeLa**-CD4-LTR- β -Gal. By coincubation with CD4-pos. T cells such as SupT1, A2.01-Env cells were observed to mediate rapidly numerous well-defined syncytia in a reproducible fashion. By expressing *****Tat*****, they also had the capacity to trans-activate the LTR-linked reporter β -Gal gene following fusion with **HeLa**-CD4-LTR- β -Gal cells. The fusion-inhibiting anti-CD4 monoclonal antibodies Q425 and Q428 were used to block specifically Env-mediated fusion with CD4-pos. cells and to demonstrate application of this system to the search for potential fusion-blocking agents. Our system thus offers a biol. significant model for studying fusion events with the advantages of being rapid, reproducible, and versatile.

ACCESSION NUMBER: 1996:19715 CAPLUS

DOCUMENT NUMBER: 124:105735

TITLE: Characterization of siamycin I, a human immunodeficiency virus fusion inhibitor

AUTHOR(S): Lin, Ping-Fang; Samanta, Himadri; Bechtold, Clifford M.; Deminie, Carol A.; Patick, Amy K.; Alam, Masud; Riccardi, Keith; Rose, Ronald E.; White, Richard J.; Colonna, Richard J.

CORPORATE SOURCE: Dep. Virol., Bristol-Myers Squibb Pharmaceutical Res. Inst., Wallingford, CT, 06492, USA

SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(1), 133-8

CODEN: AMACCO; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The human immunodeficiency virus (HIV) fusion inhibitor siamycin I, a 21-residue tricyclic peptide, was identified from a *Streptomyces* culture by using a cell **fusion assay** involving cocultivation of ***HeLa*** -CD4+ cells and monkey kidney (BSC-1) cells expressing the HIV envelope gp160. Siamycin I is effective against acute HIV type 1 (HIV-1) and HIV-2 infections, with 50% EDs ranging from 0.05 to 5.7 μ M, and the concentration resulting in a 50% decrease in cell viability in the absence of viral infection is 150 μ M in CEM-SS cells. Siamycin I inhibits fusion between C8166 cells and CEM-SS cells chronically infected with HIV (50% ED of 0.08 μ M) but has no effect on Sendai virus-induced fusion or murine myoblast fusion. Siamycin I does not inhibit gp120 binding to CD4 in either gp120- or CD4-based capture enzyme-linked immunosorbent assays. Inhibition of HIV-induced fusion by this compound is reversible, suggesting that siamycin I binds noncovalently. An HIV-1 resistant variant was selected by in vitro passage of virus in the presence of increasing concns. of siamycin I. Drug susceptibility studies on a chimeric virus containing the envelope gene from the siamycin I-resistant variant indicate that resistance maps to the gp160 gene. Envelope-deficient HIV complemented with gp160 from siamycin I-resistant HIV also displayed a resistant phenotype upon infection of **HeLa**-CD4-LTR- β -gal cells. A comparison of the DNA sequences of the envelope genes from the resistant and parent viruses revealed a total of six amino acid changes. Together these results indicate that siamycin I interacts with the HIV envelope protein.

ACCESSION NUMBER: 1996:19715 CAPLUS

DOCUMENT NUMBER: 124:105735

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AUTHOR(S): Lin, Ping-Fang; Samanta, Himadri; Bechtold, Clifford M.; Deminie, Carol A.; Patick, Amy K.; Alam, Masud; Riccardi, Keith; Rose, Ronald E.; White, Richard J.; Colonna, Richard J.

CORPORATE SOURCE: Dep. Virol., Bristol-Myers Squibb Pharmaceutical Res. Inst., Wallingford, CT, 06492, USA

SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(1), 133-8

CODEN: AMACCO; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

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ACCESSION NUMBER: 1996:438785 CAPLUS

DOCUMENT NUMBER: 125:136768

TITLE: Expression of HIV env gene in a human T cell line for
a rapid and quantifiable cell **fusion**
assay

AUTHOR(S): Moir, Susan; Poulin, Louise

CORPORATE SOURCE: Faculty Medicine, Laval University, Ste-Foy, QC, G1V
4G2, Can.

SOURCE: AIDS Research and Human Retroviruses (1996), 12(9),
811-820

CODEN: ARHRE7; ISSN: 0889-2229

PUBLISHER: Liebert

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins present at the surface of infected cells are known to mediate fusion with CD4-pos. target cells. In this study we have developed a novel Env-expressing cell line for investigating the fusion process in a biol. significant system. Cell surface expression of the HIV-1 env gene, isolated from the highly fusogenic strain SF33, was obtained in the CD4-neg. T cell line A2.01. To render the system versatile and efficient, HIV-1 regulatory proteins Tat and Rev were supplied in trans. The presence of Env at the cell surface was shown by cytofluorometry and immunofluorescence and precursor processing of gp160 to gp120/gp41 was demonstrated by Western blot. The fusion capacity of A2.01-Env cells was assessed by coculture with CD4-pos. T lymphocytes or the fusion indicator cell line, **HeLa**-CD4-LTR- β -Gal. By coincubation with CD4-pos. T cells such as SupT1, A2.01-Env cells were observed to mediate rapidly numerous well-defined syncytia in a reproducible fashion. By expressing Tat, they also had the capacity to trans-activate the LTR-linked reporter β -Gal gene following fusion with **HeLa**-CD4-LTR- β -Gal cells. The fusion-inhibiting anti-CD4 monoclonal antibodies Q425 and Q428 were used to block specifically Env-mediated fusion with CD4-pos. cells and to demonstrate application of this system to the search for potential fusion-blocking agents. Our system thus offers a biol. significant model for studying fusion events with the advantages of being rapid, reproducible, and versatile.

ACCESSION NUMBER: 2003:900264 CAPLUS
DOCUMENT NUMBER: 140:92158
TITLE: Establishment of an HIV cell-cell **fusion assay** by using two genetically modified **HeLa** cell lines and reporter gene
AUTHOR(S): Sakamoto, Tatsunori; Ushijima, Hiroshi; Okitsu, Shoko; Suzuki, Eiko; Sakai, Koji; Morikawa, Shigeru; Muller, Werner E. G.
CORPORATE SOURCE: Graduate School of Medicine, Department of Developmental Medical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan
SOURCE: Journal of Virological Methods (2003), 114(2), 159-166
CODEN: JVMEDH; ISSN: 0166-0934
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:

Infection of human cells with the human immunodeficiency virus type I (HIV-1) can be mimicked by a fusion process between cells expressing the HIV envelope protein (Env) and cells expressing both human CD4 together with the appropriate human chemokine receptors. In this study, a T-tropic HIV cell-cell *****fusion*** assay** was established that utilized CD4, human CXCR4 and HIV NL4-3 gp160 as fusion components and a T7 polymerase-activated luciferase as a reporter system. The **HeLa** T4 cells used, expressed CD4 and CXCR4, and the applied **HeLa** KS386 cells expressed HIV NL4-3 gp160. By combining **HeLa** T4 cells with **HeLa** KS386 cells, an approx. about 100- to 300-fold increase in luciferase activity could be elicited relative to the control. The addition of anti-CD4 monoclonal antibody (Mab) (RPA-T4) or anti-CXCR4 Mab (12G5) in the assay significantly inhibited the fusion event; in contrast, an anti-CCR5 Mab (2D7) had no effect, indicating that the **fusion assay** was CD4 and CXCR4 dependent. In this report, fusion events could be monitored by both the luciferase reporter system and syncytia formation. Fusion events were monitored and compared using these two approaches. The luciferase reporter system was found to be more sensitive than syncytia formation. Moreover, compared with previous HIV fusion models, such as using recombinant vaccinia viruses, this system has several advantages, including simplicity and sensitivity. Finally, the system provides a powerful tool to study fusion mechanisms mediated by T-tropic HIV gp160, as well as to screen for fusion-blocking antibodies and antiviral agents.

ACCESSION NUMBER: 1999:379817 CAPLUS
 DOCUMENT NUMBER: 131:183689
 TITLE: Role of the HIV type 1 glycoprotein 120 V3 loop in determining coreceptor usage
 AUTHOR(S): Verrier, Florence; Borman, Andrew M.; Brand, Denys; Girard, Marc
 CORPORATE SOURCE: Unite de Virologie Moleculaire (CNRS URA 1966), Departement de Virologie, Institut Pasteur, Paris, 75724, Fr.
 SOURCE: AIDS Research and Human Retroviruses (1999), 15(8), 731-743
 CODEN: ARHRE7; ISSN: 0889-2229
 PUBLISHER: Mary Ann Liebert, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

ABSTRACT:

Macrophage (M)-tropic HIV-1 isolates use the β -chemokine receptor CCR5 as a coreceptor for entry, while T cell line-adapted (TCLA) strains use CXCR4 and dual-tropic strains can use either CCR5 or CXCR4. To investigate the viral determinants involved in choice of coreceptor, we used a **fusion** ***assay*** based on the infection of CD4+ **HeLa** cells that express one or both coreceptors with Semliki Forest virus (SFV) recombinants expressing the native HIV-1 gp160 of a primary M-tropic isolate (HIV-1BX08), a TCLA isolate (HIV-1LAI), or a dual-tropic strain (HIV-1MN). We examined whether the V3 region of these glycoproteins interacts directly with the corresponding coreceptors by assaying coreceptor-dependent cell-to-cell fusion mediated by the different recombinants in the presence of various synthetic linear peptides. Synthetic peptides corresponding to different V3 loop sequences blocked syncytium formation in a coreceptor-specific manner. Synthetic V2 peptides were also inhibitory for syncytium formation, but showed no apparent coreceptor specificity. A BX08 V3 peptide with a D320 \rightarrow R substitution retained no inhibitory capacity for BX08 Env-mediated cell-to-cell fusion, but inhibited LAI Env-mediated fusion as efficiently as the homologous LAI V3 peptide. The same mutation engineered in the BX08 env gene rendered it able to form syncytia on CD4+CXCR4+CCR5- **HeLa** cells and susceptible to inhibition by SDF-1 α and MIP-1 β . Other substitutions tested (D320 \rightarrow Q/D324 \rightarrow N or S306 \rightarrow R) exhibited intermediate effects on coreceptor usage. These results underscore the importance of the V3 loop in modulating coreceptor choice and show that single amino acid modifications in V3 can dramatically modify coreceptor usage. Moreover, they provide evidence that linear V3 loop peptides can compete with intact cell surface-expressed gp120/gp41 for CCR5 or CXCR4 interaction

L7 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:495370 CAPLUS

DOCUMENT NUMBER: 125:163144

TITLE: Human immunodeficiency virus type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer

AUTHOR(S): Litwin, Virginia; Nagashima, Kirsten A.; Ryder, Andrew M.; Chang, Chun-Huey; Carver, Jeffrey M.; Olson, William C.; Alizon, Marc; Hasel, Karl W.; Maddon, Paul J.; Allaway, Graham P.

CORPORATE SOURCE: Progenics Pharmaceuticals, Inc., Tarrytown, NY, 10591, USA

SOURCE: Journal of Virology (1996), 70(9), 6437-6441
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory adapted T-lymphotropic strains of the virus. The goal of this study was to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory adapted strain. To this end, a new **fusion assay** was developed on the basis of the principle of resonance energy transfer, using *****HeLa***** cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1LAI or the macrophage-tropic primary isolate HIV-1JR-FL. These cells fused with CD4+ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, **HeLa** cells expressing HIV-1JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate tht the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1JR-FL and HIV-1LAI in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar; fusion occurred at neutral pH and was dependent on the presence of divalent cations. Inhibition of HIV-1JR-FL envelope glycoprotein-mediated membrane fusion by soluble CD4 and CD4-IgG2 occurred at concns. similar to those required to neutralize this virus. Higher concns. of these agents were required to inhibit HIV-1LAI envelope glycoprotein-mediated membrane fusion, in contrast to the greater sensitivity of HIV-1LAI virions to neutralization by soluble CD4 and CD4-IgG2. This finding suggests that the mechanisms of fusion inhibition and

ACCESSION NUMBER: 1998:115164 CAPLUS
DOCUMENT NUMBER: 128:216242
TITLE: Identification of determinants on a dualtropic human immunodeficiency virus type 1 envelope glycoprotein that confer usage of CXCR4
AUTHOR(S): Cho, Michael W.; Lee, Myung K.; Carney, Michelle C.; Berson, Joanne F.; Doms, Robert W.; Martin, Malcolm A.
CORPORATE SOURCE: Lab. of Mol. Microbiol., Natl. Inst. of Allergy and Infect. Dis., Natl. Inst. of Health, Bethesda, MD, 20892-0460, USA
SOURCE: ~~Journal of Virology (1998), 72(3), 2509-2515~~
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

ABSTRACT:

The chemokine receptors CCR5 and CXCR4, in combination with CD4, mediate cellular entry of macrophage-tropic (M-tropic) and T-cell-tropic strains of human immunodeficiency virus type 1 (HIV-1), resp., while dualtropic viruses can use either receptor. The authors have constructed a panel of chimeric viruses and envelope glycoproteins in which various domains of the dualtropic HIV-1DH12 gp160 were introduced into the genetic background of an M-tropic HIV-1 isolate, HIV-1AD8. These constructs were employed in cell fusion and virus infectivity assays using peripheral blood mononuclear cells, MT4 T cells, primary monocyte-derived macrophages, or HOS-CD4 cell lines, expressing various chemokine receptors, to assess the contributions of different gp120 subdomains in coreceptor usage and cellular tropism. As expected, the dualtropic HIV-1DH12 gp120 utilized either CCR3, CCR5, or CXCR4, whereas HIV-1AD8 gp120 was able to use only CCR3 or CCR5. The authors found that either the V1/V2 or the V3 region of HIV-1DH12 gp120 individually conferred on HIV-1AD8 the ability to use CXCR4, while the combination of both the V1/V2 and V3 regions increased the efficiency of CXCR4 use. In addition, while the V4 or the V5 region of HIV-1DH12 gp120 failed to confer the capacity to utilize CXCR4 on HIV-1AD8, these regions were required in conjunction with regions V1 to V3 of HIV-1DH12 gp120 for efficient utilization of CXCR4. Comparison of virus infectivity analyses with various cell types and cell ***fusion*** assays revealed assay-dependent discrepancies and indicated that events occurring at the cell surface during infection are complex and cannot always be predicted by any one assay.

ACCESSION NUMBER: 2001:887689 CAPLUS

DOCUMENT NUMBER: 136:193711

TITLE: Inhibitory effects of small-molecule **CCR5** antagonists on human immunodeficiency virus type 1 envelope-mediated membrane fusion and viral replication

AUTHOR(S): Takashima, Katsunori; Miyake, Hiroshi; Furuta, Rika A.; Fujisawa, Jun-Ichi; Iizawa, Yuji; Kanzaki, Naoyuki; Shiraishi, Mitsuru; Okonogi, Kenji; Baba, Masanori

CORPORATE SOURCE: Division of Human Retroviruses, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University, Kagoshima, 890-8520, Japan

SOURCE: Antimicrobial Agents and Chemotherapy (2001), 45(12), 3538-3543

CODEN: AMACQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

We established a human immunodeficiency virus type 1 (HIV-1) envelope (Env)-mediated membrane **fusion assay** and examined the small-mol. **CCR5** antagonist TAK-779 and its derivs. for their inhibitory effects on HIV-1 Env-mediated membrane fusion and viral replication. The membrane **fusion assay** is based on HIV-1 long terminal repeat-directed β -D-galactosidase reporter gene expression in CD4- and ***CCR5*** -expressed HeLa (MAGI-**CCR5**) cells after cocultivation with effector 293T cells expressing HIV-1 Env. Inhibition of HIV-1 replication was also determined in MAGI-**CCR5** cells infected with the corresponding cell-free HIV-1. TAK-779 effectively suppressed R5 HIV-1 (strain JR-FL) Env-mediated membrane fusion as well as viral replication. Its 50% inhibitory concns. (IC50s) for membrane fusion and viral replication were 0.87 ± 0.11 and 1.4 ± 0.1 nM, resp. These values corresponded well to the IC50 for 125I-RANTES (regulated on activation, T cell expressed, and secreted) binding to **CCR5** (1.4 nM). The inhibitory effects of 18 TAK-779 derivs. on membrane fusion differed from one compound to another. However, there was a close correlation among their inhibitory effects on membrane fusion, viral replication, and RANTES binding. The correlation coefficient between their IC50s for membrane fusion and viral replication was 0.881. Furthermore, since this assay depends on Env expressed in the effector cells, it is also applicable to the evaluation of CXCR4 antagonists. These results indicate that the HIV-1 Env-mediated membrane **fusion assay** is a useful tool for the evaluation of entry **inhibitors**

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:455171 CAPLUS

DOCUMENT NUMBER: 139:67648

TITLE: Human immunodeficiency virus type 1 entry
inhibitors selected on living cells from a
library of phage chemokines

AUTHOR(S): Hartley, Oliver; Dorgham, Karim; Perez-Bercoff,
Danielle; Cerini, Fabrice; Heimann, Anouk; Gaertner,
Hubert; Offord, Robin E.; Pancino, Gianfranco; Debre,
Patrice; Gorochov, Guy

CORPORATE SOURCE: Immunologie A., CERVI, INSERM U543, Hospital
Pitie-Salpetriere, Paris, Fr.

SOURCE: Journal of Virology (2003), 77(12), 6637-6644
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The chemokine receptors **CCR5** and **CXCR4** are promising non-virus-encoded targets for human immuno-deficiency virus (HIV) therapy. We describe a selection procedure to isolate mutant forms of RANTES (CCL5) with antiviral activity considerably in excess of that of the native chemokine. The phage-displayed library of randomly mutated and N-terminally extended variants was screened by using live **CCR5**-expressing cells, and two of the selected mutants, P1 and P2, were further characterized. Both were significantly more potent HIV **inhibitors** than RANTES, with P2 being the most active (50% inhibitory concentration of 600 pM in a viral coat-mediated cell

fusion **assay**, complete protection of target cells against primary HIV type 1 strains at a concentration of 10 nM). P2 resembles AOP-RANTES in that it is a superagonist of **CCR5** and potently induces receptor sequestration. P1, while less potent than P2, has the advantage of significantly reduced signaling activity via **CCR5** (30% of that of RANTES). Addnl., both P1 and P2 exhibit not only significantly increased affinity for **CCR5** but also enhanced receptor selectivity, retaining only trace levels of signaling activity via CCR1 and CCR3. The phage chemokine approach that was successfully applied here could be adapted to other chemokine-chemokine receptor systems and used to further improve the first-generation mutants reported in this paper.

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:115164 CAPLUS

DOCUMENT NUMBER: 128:216242

TITLE: Identification of determinants on a dualtropic human immunodeficiency virus type 1 envelope glycoprotein that confer usage of CXCR4

AUTHOR(S): Cho, Michael W.; Lee, Myung K.; Carney, Michelle C.; Berson, Joanne F.; Doms, Robert W.; Martin, Malcolm A.

CORPORATE SOURCE: Lab. of Mol. Microbiol., Natl. Inst. of Allergy and Infect. Dis., Natl. Inst. of Health, Bethesda, MD, 20892-0460, USA

SOURCE: Journal of Virology (1998), 72(3), 2509-2515

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The chemokine receptors CCR5 and CXCR4, in combination with CD4, mediate cellular entry of macrophage-tropic (M-tropic) and T-cell-tropic strains of human immunodeficiency virus type 1 (HIV-1), resp., while dualtropic viruses can use either receptor. The authors have constructed a panel of chimeric viruses and envelope glycoproteins in which various domains of the dualtropic HIV-1DH12 gp160 were introduced into the genetic background of an M-tropic HIV-1 isolate, HIV-1AD8. These constructs were employed in cell fusion and virus infectivity assays using peripheral blood mononuclear cells, MT4 T cells, primary monocyte-derived macrophages, or HOS-CD4 cell lines, expressing various chemokine receptors, to assess the contributions of different gp120 subdomains in coreceptor usage and cellular tropism. As expected, the dualtropic HIV-1DH12 gp120 utilized either CCR3, CCR5, or CXCR4, whereas HIV-1AD8 gp120 was able to use only CCR3 or CCR5. The authors found that either the V1/V2 or the V3 region of HIV-1DH12 gp120 individually conferred on HIV-1AD8 the ability to use CXCR4, while the combination of both the V1/V2 and V3 regions increased the efficiency of CXCR4 use. In addition, while the V4 or the V5 region of HIV-1DH12 gp120 failed to confer the capacity to utilize CXCR4 on HIV-1AD8, these regions were required in conjunction with regions V1 to V3 of HIV-1DH12 gp120 for efficient utilization of CXCR4. Comparison of virus infectivity analyses with various cell types and cell ***fusion*** assays revealed assay-dependent discrepancies and indicated that events occurring at the cell surface during infection are complex and cannot always be predicted by any one assay.

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:731875 CAPLUS

DOCUMENT NUMBER: 140:138613

TITLE: Development of a novel high-throughput surrogate assay to measure HIV envelope/CCR5/CD4-mediated viral/cell fusion using BacMam baculovirus technology

AUTHOR(S): Jenkinson, Stephen; McCoy, David C.; Kerner, Sandy A.; Ferris, Robert G.; Lawrence, Wendell K.; Clay, William C.; Condreay, J. Patrick; Smith, Chari D.

CORPORATE SOURCE: GlaxoSmithKline Research and Development, Research Triangle Park, NC, USA

SOURCE: Journal of Biomolecular Screening (2003), 8(4), 463-470

CODEN: JBISF3; ISSN: 1087-0571

PUBLISHER: Sage Publications

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The initial event by which M-tropic HIV strains gain access to cells is via interaction of the viral envelope protein gp120 with the host cell CCR5 co-receptor and CD4. Inhibition of this event reduces viral fusion and entry into cells in vitro. The authors have employed BacMam baculovirus-mediated gene transduction to develop a cell/cell **fusion assay** that mimics the HIV viral/cell fusion process and allows high-throughput quantification of this fusion event. The assay design uses human osteosarcoma (HOS) cells stably transfected with cDNAs expressing CCR5, CD4, and long terminal repeat (LTR)-luciferase as the recipient host cell. An HEK-293 cell line transduced with BacMam viral constructs to express the viral proteins gp120, gp41, tat, and rev represents the virus. Interaction of gp120 with CCR5/CD4 results in the fusion of the 2 cells and transfer of tat to the ***HOS*** cell cytosol; tat, in turn, binds to the LTR region on the luciferase reporter and activates transcription, resulting in an increase in cellular luciferase activity. In conclusion, the cell/cell **fusion** ***assay*** developed has been demonstrated to be a robust and reproducible high-throughput surrogate assay that can be used to assess the effects of compds. on gp120/CCR5/CD4-mediated viral fusion into host cells.

L14 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:717667 CAPLUS

DOCUMENT NUMBER: 132:220905

TITLE: Blocking HIV co-receptors by chemokines

AUTHOR(S): Virelizier, J. L.

CORPORATE SOURCE: Unite d'Immunologie Virale, Institut Pasteur, Paris, Fr.

SOURCE: Developments in Biological Standardization (1999), 97(Biological Characterization and Assay of Cytokines and Growth Factors), 105-109
CODEN: DVBSA3; ISSN: 0301-5149

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ABSTRACT:

A review with 15 refs. Specific chemokines can block HIV entry and replication because they antagonize the common strategy of lentiviruses to use chemokine receptors for infecting CD4+ cells of the body, especially lymphocytes and cells of the monocytic lineage. This raised intense academic and therapeutic interest. The antiviral potency of these chemokines is indeed remarkable, but depends on the chemokine and the HIV isolate used. This is because HIV appears to use many co-receptors, alternatively or in addition to the CCR5 co-receptor. These include CCR3, CXCR4, STRL33/Bonzo/TYMSTR, and BOB. The CC chemokines ***RANTES***, MIP-1 α , MIP-1 β , and eotaxin can suppress the replication of CCR5- and CCR3-dependent viruses, while SDF-1 α/β suppresses that of CXCR4-dependent strains. Although no general rule can be drawn at present, it appears that chronic HIV infection may give rise to viruses which, instead of using preferentially or exclusively CCR5, are capable of using more than one co-receptor. This underlines the need for assaying the tropism of primary isolates, using both **fusion assays** and protection of activated lymphocyte cultures by one or more antiviral chemokines or chemokine antagonists.

ACCESSION NUMBER: 1994:1877 CAPLUS
 DOCUMENT NUMBER: 120:1877
 TITLE: Genomic organization and transcriptional regulation of the **RANTES** chemokine gene
 AUTHOR(S): Nelson, Peter J.; Kim, Hubert T.; Manning, William C.; Goralski, Thomas J.; Krensky, Alan M.
 CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
 SOURCE: Journal of Immunology (1993), 151(5), 2601-12
 CODEN: JOIMA3; ISSN: 0022-1767
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 ABSTRACT:

RANTES is a member of a large supergene family of pro-inflammatory cytokines called CC chemokines that appear to play a fundamental role in inflammatory processes. The **RANTES** protein causes release of histamine from basophils and is a chemoattractant for CD45RO/CD4+ "memory" T lymphocytes, monocytes, and eosinophils. Although expression of **RANTES** was first thought to be limited to activated T cells, recent data have shown that it is produced by a variety of tissue types in response to specific stimuli. **RANTES** mRNA is expressed late (3 to 5 days) after activation of resting T cells whereas in fibroblasts, renal epithelial and mesangial cells, **RANTES** mRNA is quickly up-regulated by TNF- α stimulation. In order to gain a better understanding of the mol. mechanisms that regulate expression of the **RANTES** locus, the authors have characterized the **RANTES** gene and determined a putative promoter region. The **RANTES** gene spans approx. 7.1 kb and is composed of three exons of 133, 112 and 1075 bases and two introns of approx. 1.4 and 4.4 kb with the position of intron/exon boundaries conserved relative to the other CC chemokine family members. Approx. 1 kb of DNA from the immediate 5' upstream region of *****RANTES***** was sequenced and found to contain a large number of potential consensus elements for specific T cell/hemopoietic, myeloid, muscle, and ubiquitously expressed DNA-binding factors. **RANTES** -promoter-luciferase gene fusion assays demonstrate high levels of reporter gene activity in a "mature" T cell line Hut78, the erythroleukemic cell line HEL, and the rhabdomyosarcoma cell line RD, with little or no activity in the "early" T cell line Jurkat, the $\gamma\delta$ T cell line PEER, the thymic tumor Molt4, or the pre-erythroid cell line K562. Deletion anal. of the promoter region indicates that different transcriptional mechanisms control expression of **RANTES** in the various tissues studied.



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 Search numbers may not be continuous; all searches are represented.
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#42	Search Mori S 1996 and HIV Limits: Publication Date to 1996/05/20	13:49:39	1
#36	Search Allowway GP 1996 and HIV Limits: Publication Date to 1996/05/20	13:48:34	30
#40	Search Allowway GP 1996 and membrane fusion Limits: Publication Date to 1996/05/20	13:48:19	2
#39	Search Allowway GP 1996 and HIV and hela Limits: Publication Date to 1996/05/20	13:47:05	1
#37	Search Allowway GP 1996 and HIV and fusion Limits: Publication Date to 1996/05/20	13:46:43	1
#35	Search Allowway GP 1996 Limits: Publication Date to 1996/05/20	13:44:53	330
#34	Search Graham P 1996 Limits: Publication Date to 1996/05/20	13:44:14	5
#33	Search Litwin V 1996 Limits: Publication Date to 1996/05/20	13:43:57	0
#32	Search Colonno RJ 1996 Limits: Publication Date to 1996/05/20	13:41:19	3
#31	Search CD4 and CXCR4 Limits: Publication Date to 1996/05/20	13:37:07	3
#29	Search HIV fusion and CXCR4 Limits: Publication Date to 1996/05/20	13:36:42	3
#28	Search HIV fusion assay and CXCR4 Limits: Publication Date to 1996/05/20	13:36:31	0
#26	Search HIV fusion assay and CCR5 Limits: Publication Date to 1996/05/20	13:36:24	0
#27	Search HIV fusion assay and chemokine receptor Limits: Publication Date to 1996/05/20	13:36:15	0
#25	Search HIV fusion assay Limits: Publication Date to 1996/05/20	13:35:55	465

by these findings are now being pursued to obtain information regarding the relative locations of the active sites of HN and to further elucidate the relationship between the receptor-binding and receptor-destroying activities of HN during the viral life cycle. The quantitative assay that we describe is of immediate applicability to large-scale screening for potential inhibitors of HPF3 infection in vivo.

L8 ANSWER 6 OF 6 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1997:42494 BIOSIS
DOCUMENT NUMBER: PREV199799334482
TITLE: Expression of HIV env gene in a human T cell line for a rapid and quantifiable cell **fusion assay**
AUTHOR(S): Moir, Susan; Poulin, Louise [Reprint author]
CORPORATE SOURCE: Infectiol., Cent. Recherche du CHUL, 2705 Boul. Laurier, Ste-Foy, Quebec G1V 4G2, Canada
SOURCE: AIDS Research and Human Retroviruses, (1996) Vol. 12, No. 9, pp. 811-820.
CODEN: ARHRE7. ISSN: 0889-2229.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997

AB Human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins present at the surface of infected cells are known to mediate fusion with CD4-positive target cells. In this study we have developed a novel Env-expressing cell line for investigating the fusion process in a biologically significant system. Cell surface expression of the HIV-1 env gene, isolated from the highly fusogenic strain SF33, was obtained in the CD4-negative T cell line A2.01. To render the system versatile and efficient, HIV-1 regulatory proteins **Tat** and **Rev** were supplied in trans. The presence of Env at the cell surface was shown by cytofluorometry and immunofluorescence and precursor processing of gp160 to gp120/gp41 was demonstrated by Western blot. The fusion capacity of A2.01-Env cells was assessed by coculture with CD4-positive T lymphocytes or the fusion indicator cell line, **HeLa**-CD4-LTR-beta-Gal. By coincubation with CD4-positive T cells such as SupT1, A2.01-Env cells were observed to mediate rapidly numerous well-defined syncytia in a reproducible fashion. By expressing **Tat**, they also had the capacity to trans-activate the LTR-linked reporter beta-Gal gene following fusion with **HeLa**-CD4-LTR-beta-Gal cells. The fusion-inhibiting anti-CD4 monoclonal antibodies Q425 and Q428 were used to block specifically Env-mediated fusion with CD4-positive cells and to demonstrate application of this system to the search for potential fusion-blocking agents. Our system thus offers a biologically significant model for studying fusion events with the advantages of being rapid, reproducible, and versatile.

L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:469926 CAPLUS

DOCUMENT NUMBER: 141:64289

TITLE: HIV-chemotherapy and -prophylaxis: new drugs, leads and approaches

AUTHOR(S): De Clercq, Erik

CORPORATE SOURCE: K.U. Leuven, Rega Institute for Medical Research, Louvain, B-3000, Belg.

SOURCE: International Journal of Biochemistry & Cell Biology (2004), 36(9), 1800-1822

CODEN: IJBBFU; ISSN: 1357-2725

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. In recent years, significant progress has been made towards the chemotherapy (and prophylaxis) of HIV infections. This progress is situated at three different levels. (i) New anti-HIV drugs have been approved for clin. use and have entered the market: the **virus entry inhibitor** enfuvirtide (Fuzeon), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (Emtriva), the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir disoproxil fumarate (Viread) and the HIV protease inhibitor (PI) atazanavir (Reyataz). (ii) Other compds. have proceeded through preclin. and/or clin. development: **CXCR4** antagonists (i.e. AMD070), CCR5 antagonists (i.e. SCH-C), NRTIs (such as amdoxovir), NNRTIs (such as etravirine), integrase inhibitors (such as S-1360) and PIs (such as tipranavir). (iii) Yet other compds., acting by novel mechanisms, have recently been identified as anti-HIV agents that seem worthy of further (pre)clin. development: cell receptor CD4 down-modulators (i.e. cyclotriazadisulfonamides), viral envelope gp120-binding agents such as plant lectins and glycopeptide antibiotics, HIV integrase inhibitors such as the pyranodipyrimidine V-165, and two new classes of compds. (i.e. N-aminoimidazoles and pyridine oxide derivs.) which seem to interfere with a post-integration, transcription transactivation event. Taken together, it is obvious that the approaches for the treatment of HIV infections in recent years have become both more diverse and more efficient.

REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L4 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:464444 BIOSIS
DOCUMENT NUMBER: PREV200300464444
TITLE: HIV coreceptors: Role of structure, posttranslational
modifications, and internalization in viral-cell fusion and
as targets for entry inhibitors.
AUTHOR(S): Zaitseva, Marina; Peden, Keith; Golding, Hana [Reprint
Author]
CORPORATE SOURCE: Division of Viral Products, Center for Biologics Evaluation
and Research, Food and Drug Administration, 8800 Rockville
Pike, Bethesda, MD, 20892, USA
goldingH@cber.fda.gov
SOURCE: Biochimica et Biophysica Acta, (11 July 2003) Vol. 1614,
No. 1, pp. 51-61. print.
ISSN: 0006-3002 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 2003
Last Updated on STN: 8 Oct 2003

AB The human immunodeficiency virus (HIV) envelope glycoprotein forms trimers
on the virion surface, with each monomer consisting of two subunits, gp120
and gp41. The gp120 envelope component binds to CD4 on target cells and
undergoes conformational changes that allow gp120 to interact with certain
G-protein-coupled receptors (GPCRs) on the same target membranes. The
GPCRs that function as HIV coreceptors were found to be chemokine
receptors. The primary coreceptors are CCR5 and CXCR4, but several other
chemokine receptors were identified as "minor coreceptors", indicating
their ability support entry of some HIV strains in tissue cultures.
Formation of the trimolecular complexes stabilizes virus binding and
triggers a series of conformational changes in gp41 that facilitate
membrane fusion and viral cell entry. Concerted efforts are underway to
decipher the specific interactions between gp120/CD4, gp120/coreceptors,
and their contributions to the subsequent membrane fusion process. It is
hoped that some of the transient conformational intermediates in gp120 and
gp41 would serve as targets for entry inhibitors. In addition, the CD4
and coreceptors are primary targets for several classes of inhibitors
currently under testing. Our review summarizes the current knowledge on
the interactions of HIV gp120 with its receptor and coreceptors, and the
important properties of the chemokine receptors and their regulation in
primary target cells. We also summarize the classes of coreceptor
inhibitors under development.

L4 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:520523 BIOSIS
DOCUMENT NUMBER: PREV200200520523
TITLE: A rapid multi-functional HIV-1 entry assay for measuring
drug susceptibility, co-receptor tropism, and antibody
neutralization.
AUTHOR(S): Huang, W. [Reprint author]; Wrin, M. T. [Reprint author];
Yap, J. [Reprint author]; Fransen, S. [Reprint author];
Beauchaine, J. [Reprint author]; Reddy, M. [Reprint
author]; Paxinos, E. E. [Reprint author]; Parkin, N. T.
[Reprint author]; Whitcomb, J. M. [Reprint author];
Petropoulos, C. J. [Reprint author]
CORPORATE SOURCE: ViroLogic, Inc., South San Francisco, CA, USA
SOURCE: Abstracts of the Interscience Conference on Antimicrobial
Agents and Chemotherapy, (2001) Vol. 41, pp. 355. print.
Meeting Info.: 41st Annual Meeting of the Interscience
Conference on Antimicrobial Agents and Chemotherapy.
Chicago, Illinois, USA. September 22-25, 2001.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 9 Oct 2002

Last Updated on STN: 9 Oct 2002

AB Inhibitors of HIV-1 entry disrupt interactions between the viral envelope proteins (gp120SU, gp41TM) and the cell surface receptor (CD4), or co-receptors (CCR5, **CXCR4**). To accelerate the development of these promising new drugs, and to assist physicians in the selection of appropriate treatment regimens, a recombinant virus assay was developed to assess entry inhibitor susceptibility and co-receptor tropism. The assay is performed by: a) generating HIV-1 particles that carry a firefly luciferase gene and are pseudotyped with patient virus encoded envelope proteins, b) infecting cells expressing CD4 plus CCR5 and/or **CXCR4**, and c) measuring luciferase production resulting from a single round of virus replication. Co-receptor tropism (X4, R5, dual) is defined by assessing the ability of the pseudotyped viruses to infect CD4-CCR5 or CD4-**CXCR4** cells. Dose dependent inhibition of R5 virus infection by R5 inhibitors is measured using CD4-CCR5 or CD4-CCR5-**CXCR4** cells. Similarly, inhibition of X4 virus infection is measured using CD4-**CXCR4** or CD4-CCR5-**CXCR4** cells. When tested separately on CD4-CCR5-**CXCR4** cells, R5 and X4 inhibitors do not fully block dual tropic virus infection. Susceptibility to fusion inhibitors can be measured in CD4 cells expressing one or both co-receptors. The IC50s of X4, R5 and fusion inhibitors vary when a single virus is tested on different cell lines and correlate with co-receptor expression. In a given cell line, the IC50s of R5, X4 and fusion inhibitors vary up to 40-fold among drug naive viruses. The assay can evaluate envelope proteins from a variety of HIV-1 subtypes (A, B, C, D, F, G). This study demonstrates that X4, R5 co-receptor tropism and virus entry inhibitor susceptibility are amenable to evaluation with recombinant virus assays. This rapid, convenient assay can also be used to measure antibody neutralization elicited by HIV vaccine candidates.

ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:520523 BIOSIS

DOCUMENT NUMBER: PREV200200520523

TITLE: A rapid multi-functional HIV-1 entry assay for measuring drug susceptibility, co-receptor tropism, and antibody neutralization.

AUTHOR(S): Huang, W. [Reprint author]; Wrin, M. T. [Reprint author]; Yap, J. [Reprint author]; Fransen, S. [Reprint author]; Beauchaine, J. [Reprint author]; Reddy, M. [Reprint author]; Paxinos, E. E. [Reprint author]; Parkin, N. T. [Reprint author]; Whitcomb, J. M. [Reprint author]; Petropoulos, C. J. [Reprint author]

CORPORATE SOURCE: ViroLogic, Inc., South San Francisco, CA, USA

SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 355. print. Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois, USA. September 22-25, 2001.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 9 Oct 2002

Last Updated on STN: 9 Oct 2002

AB Inhibitors of HIV-1 entry disrupt interactions between the viral envelope proteins (gp120SU, gp41TM) and the cell surface receptor (CD4), or co-receptors (CCR5, **CXCR4**). To accelerate the development of these promising new drugs, and to assist physicians in the selection of appropriate treatment regimens, a recombinant virus assay was developed to assess entry inhibitor susceptibility and co-receptor tropism. The assay is performed by: a) generating HIV-1 particles that carry a firefly luciferase gene and are pseudotyped with patient virus encoded envelope proteins, b) infecting cells expressing CD4 plus CCR5 and/or **CXCR4**, and c) measuring luciferase production resulting from a single round of virus replication. Co-receptor tropism (X4, R5, dual) is defined by assessing the ability of the pseudotyped viruses to infect CD4-CCR5 or CD4-**CXCR4** cells. Dose dependent inhibition of R5 virus infection by R5 inhibitors is measured using CD4-CCR5 or CD4-CCR5-**CXCR4** cells. Similarly, inhibition of X4 virus infection is measured using CD4-**CXCR4** or CD4-CCR5-**CXCR4** cells. When tested separately on CD4-CCR5-**CXCR4** cells, R5 and X4 inhibitors do not fully block dual tropic virus infection. Susceptibility to fusion inhibitors can be measured in CD4 cells expressing one or both co-receptors. The IC50s of X4, R5 and fusion inhibitors vary when a single virus is tested on different cell lines and correlate with co-receptor expression. In a given cell line, the IC50s of R5, X4 and fusion inhibitors vary up to 40-fold among drug naive viruses. The assay can evaluate envelope proteins from a variety of HIV-1 subtypes (A, B, C, D, F, G). This study demonstrates that X4, R5 co-receptor tropism and **virus entry inhibitor** susceptibility are amenable to evaluation with recombinant virus assays. This rapid, convenient assay can also be used to measure antibody neutralization elicited by HIV vaccine candidates.

L4 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:411837 BIOSIS

DOCUMENT NUMBER: PREV200100411837

TITLE: New targets for inhibitors of HIV-1 replication.

AUTHOR(S): Moore, John P. [Reprint author]; Stevenson, Mario

CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical College of Cornell University, 1300 York Avenue, New York, NY, 10021, USA

jpm2003@mail.med.cornell.edu; Mario.Stevenson@ummed.edu

SOURCE: Nature Reviews Molecular Cell Biology, (November, 2000)

Vol. 1, No. 2, pp. 40-49. print.

ISSN: 1471-0072.

DOCUMENT TYPE:

Article

General Review; (Literature Review)

LANGUAGE:

English

ENTRY DATE:

Entered STN: 29 Aug 2001

Last Updated on STN: 23 Feb 2002

ACCESSION NUMBER: 2000:191010 BIOSIS
DOCUMENT NUMBER: PREV200000191010
TITLE: Vpr-GFP virion particle identifies HIV-infected targets and preserves HIV-1Vpr function in macrophages and T-cells.
AUTHOR(S): Muthumani, Karuppiah; Montaner, Luis J.; Ayyavoo, Velpandi [Reprint author]; Weiner, D. B.
CORPORATE SOURCE: University of Pennsylvania, 422 Curie Blvd., 505 Stellar Chance Laboratories, Philadelphia, PA, 19104, USA
SOURCE: DNA and Cell Biology, (March, 2000) Vol. 19, No. 3, pp. 179-188. print.
CODEN: DCEBE8. ISSN: 1044-5498.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 May 2000
Last Updated on STN: 4 Jan 2002

AB Human immunodeficiency virus type 1 (HIV-1) is known for its ability to infect immune cells, including T-cells and macrophages. The 96-amino acid Vpr, a virion-associated protein, is essential for viral replication in monocytes/macrophages and increases viral replication in primary and established T-cell lines. The Vpr protein regulates a number of host cellular events, including proliferation, differentiation, apoptosis, cytokine production, and NF-kappaB-mediated transcription. Most of these functions have been analyzed using either endogenous Vpr protein or cells transfected with a Vpr expression plasmid. We developed a lentiviral vector complemented with a Vpr expression plasmid that results in viral particles packaged with Vpr protein. To facilitate identification of the target cells infected with the particles containing Vpr, we fused green fluorescent protein (GFP) with the Vpr open reading frame and analyzed the biology of this novel particle. Vpr itself is expressed as a 14-kDa protein; however, in vitro translation of the pVpr-GFP plasmid resulted in the expression of 39-kDa **fusion** protein. The **fusion** molecule exhibited the same activity in arresting the cell cycle in G2 as does the wildtype Vpr molecule. Subcellular localization of Vpr and Vpr-GFP by immunofluorescence in human and murine cell lines indicated that Vpr by itself or with the reporter GFP showed a peri-nuclear staining pattern. Replication kinetics showed no significant difference between Vpr-GFP and native complemented **pseudovirus** replication in a single-round infectivity assay. A flow cytometry analysis of peripheral blood lymphocytes and macrophages infected with Vpr-GFP-packaged virions and selected by GFP showed 56.7% infectivity for lymphocytes and 84.6% infectivity for macrophages. Additional analysis of CD24 (HSA)-positive cells showed infection of CD4+ cells, macrophages, and, importantly, dendritic cells. This system will allow us to identify specific cell populations including antigen-presenting cells, and allow quantitative analysis of the precise effect of Vpr on both target and bystander cells in vitro as well as in vivo.

L7 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2003:528403 BIOSIS

DOCUMENT NUMBER: PREV200300534369

TITLE: Identification of the receptor binding domain of the mouse
mammary tumor virus envelope protein.

AUTHOR(S): Zhang, Yuanming; Rassa, John C.; deObaldia, Maria Elena;
Albritton, Lorraine M.; Ross, Susan R. [Reprint Author]

CORPORATE SOURCE: University of Pennsylvania, 421 Curie Blvd., 313 BRB II,
Philadelphia, PA, 19104-6142, USA
rosss@mail.med.upenn.edu

SOURCE: Journal of Virology, (October 2003) Vol. 77, No. 19, pp.
10468-10478. print.

ISSN: 0022-538X (ISSN print).

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Nov 2003

Last Updated on STN: 12 Nov 2003

AB Mouse mammary tumor virus (MMTV) is a betaretrovirus that infects rodent cells and uses mouse transferrin receptor 1 for cell entry. To characterize the interaction of MMTV with its receptor, we aligned the MMTV envelope surface (SU) protein with that of Friend murine leukemia virus (F-MLV) and identified a putative receptor-binding domain (RBD) that included a receptor binding sequence (RBS) of five amino acids and a heparin-binding domain (HBD). Mutation of the HBD reduced virus infectivity, and soluble heparan sulfate blocked infection of cells by wild-type **pseudovirus**. Interestingly, some but not all MMTV-like elements found in primary and cultured human breast cancer cell lines, termed h-MTVs, had sequence alterations in the putative RBS. Single substitution of one of the amino acids found in an h-MTV RBS variant in the RBD of MMTV, Phe40 to Ser, did not alter species tropism but abolished both virus binding to cells and infectivity. Neutralizing anti-SU monoclonal antibodies also recognized a glutathione S-transferase **fusion** protein that contained the five-amino-acid RBS region from MMTV. The critical Phe40 residue is located on a surface of the MMTV RBD model that is distant from and may be structurally more rigid than the region of F-MLV RBD that contains its critical binding site residues. This suggests that, in contrast to other murine retroviruses, binding to its receptor may result in few or no changes in MMTV envelope protein conformation.

L1 ANSWER 19 OF 19 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2001:62035 BIOSIS

DOCUMENT NUMBER: PREV200100062035

TITLE: Aminooxypentane addition to the chemokine macrophage
inflammatory protein-1alphaP increases receptor affinities
and HIV inhibition.

AUTHOR(S): Townson, Jane R.; Graham, Gerard J.; Landau, Nathaniel R.;
Rasala, Beth; Nibbs, Robert J. B. [Reprint author]

CORPORATE SOURCE: CRC Beatson Laboratories, Beatson Institute for Cancer
Research, Switchback Road, Bearsden, Garscube Estate,
Glasgow, G61 1BD, UK
r.nibbs@beatson.gla.ac.uk

SOURCE: Journal of Biological Chemistry, (December 15, 2000) Vol.
275, No. 50, pp. 39254-39261. print.
CODEN: JBCHA3. ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 31 Jan 2001

Last Updated on STN: 12 Feb 2002

AB To enter its target cells, human immunodeficiency virus (HIV) must
interact with CD4 and one of a family of chemokine receptors. CCR5 is
widely used by the virus in this context, and its ligands can prevent HIV
entry. Amino-terminal modified chemokine variants, in particular
AOP-RANTES (aminooxypentane-linked regulated on activation normal T cell
expressed and secreted), exhibit enhanced HIV entry inhibition. We have
previously demonstrated that a non-allelic isoform of macrophage
inflammatory protein (MIP)-1alpha, termed MIP-1alphaP, is the most active
naturally occurring inhibitor of HIV entry known. Here we report the
properties of a variant of MIP-1alphaP with an AOP group on the amino
terminus. We show that, like RANTES, the addition of AOP to MIP-1alphaP
enhances its interactions with CCR1 and CCR5, allows more effective
internalization of CCR5, and increases the ligand's potency as an
inhibitor of HIV entry through CCR5. Importantly, AOP-MIP-1alphaP is
about 10-fold more active than AOP-RANTES at inhibiting HIV entry, making
it the most effective chemokine-based inhibitor of HIV entry through CCR5
described to date. Surprisingly, the enhanced receptor interactions of
AOP-MIP-1alphaP do not translate into increased chemotaxis or coupling to
calcium ion fluxes, suggesting that this protein should be viewed as a
partial, rather than a full, agonist for CCR1 and CCR5.

L1 ANSWER 18 OF 19 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2001:411837 BIOSIS

DOCUMENT NUMBER: PREV200100411837

TITLE: New targets for inhibitors of HIV-1 replication.

AUTHOR(S): Moore, John P. [Reprint author]; Stevenson, Mario

CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical
College of Cornell University, 1300 York Avenue, New York,
NY, 10021, USA

jpm2003@mail.med.cornell.edu; Mario.Stevenson@ummed.edu

SOURCE: Nature Reviews Molecular Cell Biology, (November, 2000)

Vol. 1, No. 2, pp. 40-49. print.

ISSN: 1471-0072.

DOCUMENT TYPE: Article

General Review; (Literature Review)

LANGUAGE: English

ENTRY DATE: Entered STN: 29 Aug 2001

Last Updated on STN: 23 Feb 2002

L1 ANSWER 17 OF 19 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
STN

ACCESSION NUMBER: 2002:472074 BIOSIS
DOCUMENT NUMBER: PREV200200472074
TITLE: Resistance mutation in HIV entry inhibitors.
AUTHOR(S): Hanna, Sheri L.; Yang, Chunfu; Owen, Sherry M.; Lal, Renu
B. [Reprint author]
CORPORATE SOURCE: HIV Immunology and Diagnostics Branch, 1600 Clifton Road,
Mailstop D12, Atlanta, GA, 30333, USA
RBL3@cdc.gov
SOURCE: AIDS (Hagerstown), (16 August, 2002) Vol. 16, No. 12, pp.
1603-1608. print.
CODEN: AIDSET. ISSN: 0269-9370.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002

AB Background: Two of the fusion inhibitors T-20 and 5-helix polypeptide have been shown to be potent inhibitors of cell-to-cell fusion and are currently under investigation as therapy for HIV-1. Objectives: To examine variability of HIV-1 gp41 heptads repeat regions (HR1 and HR2), with special emphasis on the presence of T-20 resistance mutations and 5-helix variability at critical epitopes, in treatment-naïve patients infected with diverse HIV-1 subtypes from different geographic regions. Methods: A total of 150 specimens representing HIV-1 group M subtypes (A-G) from persons naïve to HIV-1 viral entry inhibitor therapy were used to amplify and sequence a 506 bp segment of transmembrane protein. Results: In general, both HR1 (a.a. 540-593) and HR2 (a.a. 628-673) domains were highly conserved. Sequence analysis of the T-20 resistant domain (a.a. 547-549, GIV) revealed that 99% of the specimens (149 of 150) carried a T-20 sensitive genotype. The critical epitopes involved in the 5-helix interaction include residues at positions 628W, 631W, 635I, 638Y, 642I, 645L, 649S, 652Q, 656N, and 659E. Analysis of the 150 specimens revealed that all had identical residues at six of these positions, whereas two positions had minor variations (635 and 649) and two (645 and 659) appeared to have subtype-specific substitutions. Conclusions: This data indicates that there is limited resistance to T-20 in these worldwide populations and that the critical epitopes for effective 5-helix binding are highly conserved across all subtypes. Taken together, these data suggest that T-20 and 5-helix should provide useful additives to current antiretroviral therapy for clinical management of HIV disease.

ACCESSION NUMBER: 2002:520523 BIOSIS
DOCUMENT NUMBER: PREV200200520523
TITLE: A rapid multi-functional HIV-1 entry assay for measuring drug susceptibility, co-receptor tropism, and antibody neutralization.
AUTHOR(S): Huang, W. [Reprint author]; Wrin, M. T. [Reprint author]; Yap, J. [Reprint author]; Fransen, S. [Reprint author]; Beauchaine, J. [Reprint author]; Reddy, M. [Reprint author]; Paxinos, E. E. [Reprint author]; Parkin, N. T. [Reprint author]; Whitcomb, J. M. [Reprint author]; Petropoulos, C. J. [Reprint author]
CORPORATE SOURCE: ViroLogic, Inc., South San Francisco, CA, USA
SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 355. print. Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois, USA. September 22-25, 2001.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Oct 2002
Last Updated on STN: 9 Oct 2002
AB Inhibitors of HIV-1 entry disrupt interactions between the viral envelope proteins (gp120SU, gp41TM) and the cell surface receptor (CD4), or co-receptors (CCR5, CXCR4). To accelerate the development of these promising new drugs, and to assist physicians in the selection of appropriate treatment regimens, a recombinant virus assay was developed to assess entry inhibitor susceptibility and co-receptor tropism. The assay is performed by: a) generating HIV-1 particles that carry a firefly luciferase gene and are pseudotyped with patient virus encoded envelope proteins, b) infecting cells expressing CD4 plus CCR5 and/or CXCR4, and c) measuring luciferase production resulting from a single round of virus replication. Co-receptor tropism (X4, R5, dual) is defined by assessing the ability of the pseudotyped viruses to infect CD4-CCR5 or CD4-CXCR4 cells. Dose dependent inhibition of R5 virus infection by R5 inhibitors is measured using CD4-CCR5 or CD4-CCR5-CXCR4 cells. Similarly, inhibition of X4 virus infection is measured using CD4-CXCR4 or CD4-CCR5-CXCR4 cells. When tested separately on CD4-CCR5-CXCR4 cells, R5 and X4 inhibitors do not fully block dual tropic virus infection. Susceptibility to fusion inhibitors can be measured in CD4 cells expressing one or both co-receptors. The IC50s of X4, R5 and fusion inhibitors vary when a single virus is tested on different cell lines and correlate with co-receptor expression. In a given cell line, the IC50s of R5, X4 and fusion inhibitors vary up to 40-fold among drug naive viruses. The assay can evaluate envelope proteins from a variety of HIV-1 subtypes (A, B, C, D, F, G). This study demonstrates that X4, R5 co-receptor tropism and **virus entry inhibitor** susceptibility are amenable to evaluation with recombinant virus assays. This rapid, convenient assay can also be used to measure antibody neutralization elicited by HIV vaccine candidates

L1 ANSWER 14 OF 19 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2002:622550 BIOSIS
DOCUMENT NUMBER: PREV200200622550
TITLE: (Correction of Previews 200200472074. Variability of
critical epitopes within HIV-1 heptad repeat domains for
selected entry inhibitors in HIV-infected populations
worldwide. Correction of title.).
AUTHOR(S): Hanna, Sheri L.; Yang, Chunfu; Owen, Sherry M.; Lal, Renu
B. [Reprint author]
CORPORATE SOURCE: HIV Immunology and Diagnostics Branch, CDC, 1600 Clifton
Road, Mailstop D12, Atlanta, GA, 30333, USA
RBL3@cdc.gov
SOURCE: AIDS (Hagerstown), (6 September, 2002) Vol. 16, No. 13, pp.
1847. print.
CODEN: AIDSET. ISSN: 0269-9370.
DOCUMENT TYPE: Article
Errata
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 2002
Last Updated on STN: 12 Dec 2002

AB On page 1603 the title for this article (AIDS 2002, 16: 1603-1608) was
incorrectly printed by the publisher. The correct title should read:
Variability of critical epitopes within HIV-1 heptad repeat domains for
selected entry inhibitors in HIV-infected populations worldwide.

L1 ANSWER 15 OF 19 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on
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ACCESSION NUMBER: 2002:537365 BIOSIS
DOCUMENT NUMBER: PREV200200537365
TITLE: HIV entry inhibitors in clinical development.
AUTHOR(S): O'Hara, Bryan M. [Reprint author]; Olson, William C.
[Reprint author]
CORPORATE SOURCE: Progenics Pharmaceuticals, Inc., 777 Old Saw Mill River
Road, Tarrytown, NY, 10591, USA
bohara@progenics.com; olson@progenics.com
SOURCE: Current Opinion in Pharmacology, (October, 2002) Vol. 2,
No. 5, pp. 523-528. print.
ISSN: 1471-4892.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2002
Last Updated on STN: 16 Oct 2002

ACCESSION NUMBER: 2004:342404 CAPLUS

DOCUMENT NUMBER: 141:16900

TITLE: A target site for template-based design of measles virus entry inhibitors

AUTHOR(S): Plemper, Richard K.; Erlandson, Karl J.; Lakdawala, Ami S.; Sun, Aiming; Prussia, Andrew; Boonsombat, Jutatip; Aki-Sener, Esin; Yalcin, Ismail; Yildiz, Ilkay; Temiz-Arpaci, Ozlem; Tekiner, Betul; Liotta, Dennis C.; Snyder, James P.; Compans, Richard W.

CORPORATE SOURCE: Department of Microbiology and Immunology, School of Medicine, Emory University, Atlanta, GA, 30322, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(15), 5628-5633
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Measles virus (MV) constitutes a principal cause of worldwide mortality, accounting for almost 1 million deaths annually. Although a live-attenuated vaccine protects against MV, vaccination efficiency of young infants is low because of interference by maternal antibodies. Parental concerns about vaccination safety further contribute to waning herd immunity in developed countries, resulting in recent MV outbreaks. The development of novel antivirals that close the vaccination gap in infants and silence viral outbreaks is thus highly desirable. We previously identified a microdomain in the MV fusion protein (F protein) that is structurally conserved in the paramyxovirus family and constitutes a promising target site for rationally designed antivirals. Here we report the template-based development of a small-mol. MV inhibitor, providing proof-of-concept for our approach. This lead compound specifically inhibits fusion and spread of live MV and MV glycoprotein-induced membrane fusion. The inhibitor induces negligible cytotoxicity and does not interfere with receptor binding or F protein biosynthesis or transport but prevents F protein-induced lipid mixing. Mutations in the postulated target site alter viral sensitivity to inhibition. In silico docking of the compound in this microdomain suggests a binding model that is exptl. corroborated by a structure-activity anal. of the compound and the inhibition profile of mutated F proteins. A second-generation compound designed on the basis of the interaction model shows a 200-fold increase in antiviral activity, creating the basis for novel MV therapeutics. This template-based design approach for MV may be applicable to other clin. relevant members of the paramyxovirus family.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS

L12 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN

AB The orphan seven transmembrane domain receptor, APJ, can function as a coreceptor for cellular infection by the HIV virus. The establishment of cell lines that coexpress CD4 and APJ provide valuable tools for continuing research on HIV infection and the development of anti-HIV therapeutics.

=> D L12 IBIB ABS

L12 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:175919 CAPLUS

DOCUMENT NUMBER: 132:220881

TITLE: Animal cells presenting CD4 and the APJ receptor and their use in studies of APJ as co-receptor for HIV and the development of **inhibitors of virus binding**

INVENTOR(S): Doms, Robert; Faulds, Daryl; Hesselgesser, Joseph E.; Horuk, Richard; Mitrovic, Branislava; Zhou, Yiqing

PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany

SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014220	A1	20000316	WO 1999-EP6553	19990907
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6475718	B2	20021105	US 1998-149045	19980908
US 2002062488	A1	20020523		
CA 2341782	AA	20000316	CA 1999-2341782	19990907
AU 9959737	A1	20000327	AU 1999-59737	19990907
AU 767484	B2	20031113		
BR 9913635	A	20010522	BR 1999-13635	19990907
EP 1109906	A1	20010627	EP 1999-968679	19990907
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
RU 2225721	C2	20040320	RU 2001-109234	19990907
NO 2001001162	A	20010307	NO 2001-1162	20010307
US 2003003447	A1	20030102	US 2002-166359	20020611
US 2003008279	A1	20030109	US 2002-166113	20020611
US 2003008376	A1	20030109	US 2002-166357	20020611
US 2003008391	A1	20030109	US 2002-166372	20020611
PRIORITY APPLN. INFO.:			US 1998-149045	A 19980908
			WO 1999-EP6553	W 19990907

AB The orphan seven transmembrane domain receptor, APJ, can function as a coreceptor for cellular infection by the HIV virus. The establishment of cell lines that coexpress CD4 and APJ provide valuable tools for continuing research on HIV infection and the development of anti-HIV therapeutics.

ACCESSION NUMBER: 2002:314978 CAPLUS

DOCUMENT NUMBER: 136:319360

TITLE: Peptide **inhibitors** for modulating
respiratory syncytial virus infection and inducing
immunity based in the CX3C motif of the G glycoprotein

INVENTOR(S): Tripp, Ralph A.; Jones, Les; Anderson, Larry J.

PATENT ASSIGNEE(S): The Government of the United States of America, as
Represented by the Secretary, Department of Health and
Human Services, USA.

SOURCE: PCT Int. Appl., 70 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032942	A2	20020425	WO 2001-US32459	20011018
WO 2002032942	A3	20021212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002024416	A5	20020429	AU 2002-24416	20011018
EP 1334119	A2	20030813	EP 2001-987765	20011018
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004009177	A1	20040115	US 2003-420387	20030418
PRIORITY APPLN. INFO.:			US 2000-241521P	P 20001018
			WO 2001-US32459	W 20011018

AB Compns. and methods are provided for the treatment or prevention of respiratory syncytial virus (RSV) disease by modulating RSV infection and immunity. In particular, amino acid sequences in the RSV G glycoprotein, containing the chemokine motif defined as C-X-X-X-C (or CX3C), are identified that are essential in causing RSV infection and disease. The chemokine motif is found at amino acid positions 182-186 of native RSV G glycoprotein, and binds to the CX32C receptor (RX3CR1) on the surface of human and animal cells. The chemokine motif is biol. active and participates in **virus binding** to and infection of susceptible cells. The prevention or treatment of RSV infection is achieved by interfering with the motif, such as by administering a vaccine in which the motif is altered or by administration or induction of blocking mols. that inhibit the biol. activity of the motif. Thus, peptides containing the CX3C motif and all or a biol. active or immunogenic portion of the amino acid sequence VPCISCSNNPTC, TCWAICKRIPNK, or NKKPGKKTITTKP are shown to (1) inhibit >90% of RSV infection of susceptible cells, (2) inhibit >90% of G glycoprotein CX3C binding to CX3CR1, and (3) inhibit RSV plaque formation.

=> D L12 IBIB ABS

L12 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:175919 CAPLUS

DOCUMENT NUMBER: 132:220881

TITLE: Animal cells presenting CD4 and the APJ receptor and their use in studies of APJ as co-receptor for HIV and the development of inhibitors of virus binding

INVENTOR(S): Doms, Robert; Faulds, Daryl; Hesselgesser, Joseph E.; Horuk, Richard; Mitrovic, Branislava; Zhou, Yiqing

PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany

SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014220	A1	20000316	WO 1999-EP6553	19990907
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6475718	B2	20021105	US 1998-149045	19980908
US 2002062488	A1	20020523		
CA 2341782	AA	20000316	CA 1999-2341782	19990907
AU 9959737	A1	20000327	AU 1999-59737	19990907
AU 767484	B2	20031113		
BR 9913635	A	20010522	BR 1999-13635	19990907
EP 1109906	A1	20010627	EP 1999-968679	19990907
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
RU 2225721	C2	20040320	RU 2001-109234	19990907
NO 2001001162	A	20010307	NO 2001-1162	20010307
US 2003003447	A1	20030102	US 2002-166359	20020611
US 2003008279	A1	20030109	US 2002-166113	20020611
US 2003008376	A1	20030109	US 2002-166357	20020611
US 2003008391	A1	20030109	US 2002-166372	20020611
PRIORITY APPLN. INFO.:			US 1998-149045	A 19980908
			WO 1999-EP6553	W 19990907

AB The orphan seven transmembrane domain receptor, APJ, can function as a coreceptor for cellular infection by the HIV virus. The establishment of cell lines that coexpress CD4 and APJ provide valuable tools for continuing research on HIV infection and the development of anti-HIV therapeutics.

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:736392 CAPLUS
DOCUMENT NUMBER: 137:258523
TITLE: RNA virus-based expression vectors carrying
reporter genes and the use of pseudotyping in
their delivery to animal cells
INVENTOR(S): Kirchhoff, Frank; Muench, Jan
PATENT ASSIGNEE(S): IPF Pharmaceuticals GmbH, Germany
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074941	A1	20020926	WO 2002-EP3185	20020321
WO 2002074941	C1	20021024		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: DE 2001-10113864 A 20010321

AB The invention relates to a **reporter** virus based on lentiviruses, rhabdoviruses or foamy viruses. Such a **reporter** virus is pseudotyped using **envelope** proteins from flaviviruses, especially the hepatitis C virus, paramyxoviruses, orthomyxoviruses, arenaviruses and hepadnaviruses. Pseudotyping may be achieved using fragments or **fusion** products of the pseudotyping **envelope** protein. The invention also relates to methods for discovering substances which act against viral infections, and to methods for producing the **reporter** virus. Human and simian immunodeficiency viruses were pseudotyped with the **envelope** protein of hepatitis C virus. This was achieved by cotransformation of 293T cells with vectors for the lentivirus, with a deletion of the env gene and replacement of the nef gene with a **reporter** gene, and an **envelope** protein expression plasmid. The pseudotyped virus could infect the hepatocyte-derived HepG2 cell line.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:191010 BIOSIS
DOCUMENT NUMBER: PREV200000191010
TITLE: Vpr-GFP virion particle identifies HIV-infected
targets and preserves HIV-1Vpr function in
macrophages and T-cells.
AUTHOR(S): Muthumani, Karuppiiah; Montaner, Luis J.; Ayyavoo, Velpandi
[Reprint author]; Weiner, D. B.
CORPORATE SOURCE: University of Pennsylvania, 422 Curie Blvd., 505 Stellar
Chance Laboratories, Philadelphia, PA, 19104, USA
SOURCE: DNA and Cell Biology, (March, 2000) Vol. 19, No. 3, pp.
179-188. print.
CODEN: DCEBE8. ISSN: 1044-5498.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 May 2000
Last Updated on STN: 4 Jan 2002

AB Human immunodeficiency virus type 1 (HIV-1) is known for its ability to infect immune cells, including T-cells and macrophages. The 96-amino acid Vpr, a virion-associated protein, is essential for viral replication in monocytes/macrophages and increases viral replication in primary and established T-cell lines. The Vpr protein regulates a number of host cellular events, including proliferation, differentiation, apoptosis, cytokine production, and NF-kappaB-mediated transcription. Most of these functions have been analyzed using either endogenous Vpr protein or cells transfected with a Vpr expression plasmid. We developed a lentiviral vector complemented with a Vpr expression plasmid that results in viral particles packaged with Vpr protein. To facilitate identification of the target cells infected with the particles containing Vpr, we fused green fluorescent protein (GFP) with the Vpr open reading frame and analyzed the biology of this novel particle. Vpr itself is expressed as a 14-kDa protein; however, in vitro translation of the pVpr-GFP plasmid resulted in the expression of 39-kDa **fusion** protein. The **fusion** molecule exhibited the same activity in arresting the cell cycle in G2 as does the wildtype Vpr molecule. Subcellular localization of Vpr and Vpr-GFP by immunofluorescence in human and murine cell lines indicated that Vpr by itself or with the reporter GFP showed a peri-nuclear staining pattern. Replication kinetics showed no significant difference between Vpr-GFP and native complemented **pseudovirus** replication in a single-round infectivity assay. A flow cytometry analysis of peripheral blood lymphocytes and macrophages infected with Vpr-GFP-packaged virions and selected by GFP showed 56.7% infectivity for lymphocytes and 84.6% infectivity for macrophages. Additional analysis of CD24 (HSA)-positive cells showed infection of CD4+ cells, macrophages, and, importantly, dendritic cells. This system will allow us to identify specific cell populations including antigen-presenting cells, and allow quantitative analysis of the precise effect of Vpr on both target and bystander cells in vitro as well as in vivo.

ACCESSION NUMBER: 1996:73061 BIOSIS
DOCUMENT NUMBER: PREV199698645196
TITLE: Characterization of siamycin I, a human immunodeficiency virus fusion **inhibitor**.
AUTHOR(S): Lin, Pin-Fang [Reprint author]; Samanta, Himadri; Bechtold, Clifford M.; Deminie, Carol A.; Patick, Amy K.; Alam, Masud; Riccardi, Keith; Rose, Ronald E.; White, Richard J.; Colonna, Richard J.
CORPORATE SOURCE: Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, CT 06492, USA
SOURCE: Antimicrobial Agents and Chemotherapy, (1996) Vol. 40, No. 1, pp. 133-138.
CODEN: AMACQ. ISSN: 0066-4804.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Feb 1996
Last Updated on STN: 27 Feb 1996

AB The human immunodeficiency virus (**HIV**) **fusion inhibitor** siamycin I, a 21-residue tricyclic peptide, was identified from a Streptomyces culture by using a cell **fusion assay** involving cocultivation of HeLa-CD4+ cells and monkey kidney (BSC-1) cells expressing the **HIV** envelope gp160. Siamycin I is effective against acute **HIV** type 1 (**HIV**-1) and **HIV**-2 infections, with 50% effective doses ranging from 0.05 to 5.7 μ M, and the concentration resulting in a 50% decrease in cell viability in the absence of viral infection is 150 μ M in CEM-SS cells. Siamycin I inhibits **fusion** between C8166 cells and CEM-SS cells chronically infected with **HIV** (50% effective dose of 0.08 μ M) but has no effect on Sendai virus-induced **fusion** or murine myoblast **fusion**. Siamycin I does not inhibit gp120 binding to CD4 in either gp120- or CD4-based capture enzyme-linked immunosorbent **assays**. Inhibition of **HIV**-induced **fusion** by this compound is reversible, suggesting that siamycin I binds noncovalently. An **HIV**-1 resistant variant was selected by in vitro passage of virus in the presence of increasing concentrations of siamycin I. Drug susceptibility studies on a **chimeric** virus containing the envelope gene from the siamycin I-resistant variant indicate that resistance maps to the gp160 gene. Envelope-deficient **HIV** complemented with gp160 from siamycin I-resistant **HIV** also displayed a resistant phenotype upon infection of HeLa-CD4-LTR-beta-gal cells. A comparison of the DNA sequences of the envelope genes from the resistant and parent viruses revealed a total of six amino acid changes. Together these results indicate that siamycin I interacts with the **HIV** envelope protei

ACCESSION NUMBER: 2001:449512 BIOSIS
DOCUMENT NUMBER: PREV200100449512
TITLE: Design and properties of NCCG-gp41, a **chimeric**
gp41 molecule with nanomolar **HIV fusion**
inhibitory activity.
AUTHOR(S): Louis, John M.; Bewley, Carole A. [Reprint author]; Clore,
G. Marius
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, NIDDK, National
Institutes of Health, Bldg. 8, Bethesda, MD, 20892-0820,
USA
caroleb@intra.niddk.nih.gov; clore@speck.niddk.nih.gov
SOURCE: Journal of Biological Chemistry, (August 3, 2001) Vol. 276,
No. 31, pp. 29485-29489. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The design and characterization of a **chimeric** protein, termed
NCCG-gp41, derived from the ectodomain of human immunodeficiency virus (**HIV**), type I gp41 is described. NCCG-gp41 features an exposed
trimeric coiled-coil comprising the N-terminal helices of the gp41
ectodomain. The trimeric coiled-coil is stabilized both by **fusion**
to a minimal thermostable ectodomain of gp41 and by engineered
intersubunit disulfide bonds. NCCG-gp41 is shown to inhibit **HIV**
envelope-mediated cell **fusion** at nanomolar concentrations with
an IC50 of 16.1+-2.8 nM. It is proposed that NCCG-gp41 targets the
exposed C-terminal region of the gp41 ectodomain in its pre-hairpin
intermediate state, thereby preventing the formation of the fusogenic form
of the gp41 ectodomain, which comprises a highly stable trimer of hairpins
arranged in a six-helix bundle. NCCG-gp41 has potential as a therapeutic
agent for the direct inhibition of **HIV** cell entry, as an anti-
HIV vaccine, and as a component of a rapid throughput
assay for screening for small molecule **inhibitors** of
HIV envelope-mediated cell **fusion**. It is anticipated
that antibodies raised against NCCG-gp41 may target the trimeric
coiled-coil of N-terminal helices of the gp41 ectodomain that is exposed
in the pre-hairpin intermediate state in a manner analogous to peptides
derived from the C-terminal helix of gp41 that are currently in clinical
trials.

L18 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:25385 CAPLUS
DOCUMENT NUMBER: 130:217538
TITLE: Dissecting the mode of action of various HIV-inhibitor
classes in a stable cellular system
AUTHOR(S): Klimkait, T.; Stauffer, F.; Lupo, E.;
Sonderregger-Rubli, C.
CORPORATE SOURCE: Novartis Pharma, Inc., Basel, Switz.
SOURCE: Archives of Virology (1998), 143(11), 2109-2131
CODEN: ARVIDF; ISSN: 0304-8608
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We describe a stable and sensitive HIV evaluation system, which discriminates HIV-specific membrane **fusion** and early transcription events and is suitable for high-throughput inhibitor screening. A human lymphocytic line, constitutively producing infectious HIV-1, serves as Env-pos. donor. A second indicator cell line carries a silent HIV-1 LTR lacZ **reporter** plasmid. A bicellular cocultivation setup allows titration and standardization of "**fusion**-induced gene stimulation (FIGS)" events. With few manipulations aspects of **fusion** and/or LTR induction can be distinguished and simultaneously assayed. Anti-Env-V3 anti-bodies prevent **fusion** and subsequent lacZ induction, and a Tat-specific inhibitor blocks only lacZ induction in a dose dependent manner without affecting membrane **fusion**. The LTR **reporter** is readily activated by Tat from HIV-1, HIV-2, or **SIV** and it responds to exogenous Tat protein. The **reporter** system is sensitive enough to detect single infection events on pre-seeded layers of indicator cells, which renders it potentially useful for direct virus quantification in patients' material. Moreover, our system allows to control and normalize DNA transfection efficiencies of HIV-derived plasmids. This aspect is particularly valuable for studies of RT- and protease-inhibitors and resistances, where p24 or supernatant reverse transcriptase, otherwise standard virus readouts, can be directly affected by inhibitors or mutations.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMA

L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:390423 CAPLUS
DOCUMENT NUMBER: 131:39724
TITLE: Cytotoxin **fusion** proteins for use in killing
of cells infected by pathogens
INVENTOR(S): Dowdy, Steven F.
PATENT ASSIGNEE(S): Washington University, USA
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929721	A1	19990617	WO 1998-US26358	19981210
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2314267	AA	19990617	CA 1998-2314267	19981210
AU 9918182	A1	19990628	AU 1999-18182	19981210
EP 1037911	A1	20000927	EP 1998-963079	19981210
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
US 6221355	B1	20010424	US 1998-208966	19981210
JP 2002505077	T2	20020219	JP 2000-524312	19981210
PRIORITY APPLN. INFO.:			US 1997-69012P	P 19971210
			US 1998-82402P	P 19980420
			WO 1998-US26358	W 19981210

AB A method of controlling infection by killing infected cells is described. more **fusion** proteins that includes a transduction domain and a cytotoxic domain. The method uses **fusion** proteins of cytotoxins and a protein that directs entry into the cell (a transduction domain). The cytotoxic domain is specifically activated by a pathogen infection, e.g. by being processed by an infection-specific protease. Activation of the cytotoxin effectively kills or injures cells infected by one or a combination of different pathogens. The cytotoxin may be a protease or a prodrug-activating enzyme such as a thymidine kinase. In particular the method is directed at the treatment of HIV infection. Suitable transduction domains can be obtained from, inter alia, the tat protein, the Antennapedia gene product, and VP22 of **herpes simplex virus**. The method appears to be effective in transporting very large proteins into cells and can also tolerate a significant degree of unfolding or incorrect folding. A **fusion** protein of the TAT transduction domain and human caspase 3 (CPP-32) was shown to be effective at killing HIV-infected cells. The effect was blocked by the HIV proteinase **inhibitor** Ritonavir, and mutation of the active site cysteine to methionine.

ACCESSION NUMBER: 2000:494545 CAPLUS
DOCUMENT NUMBER: 133:234844
TITLE: Pseudorabies virus glycoprotein M inhibits membrane fusion
AUTHOR(S): Klupp, Barbara G.; Nixdorf, Ralf; Mettenleiter, Thomas C.
CORPORATE SOURCE: Institute of Molecular Biology, Federal Research Centre for Virus Diseases of Animals, Friedrich-Loeffler-Institutes, Insel Riems, D-17498, Germany
SOURCE: Journal of Virology (2000), 74(15), 6760-6768
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A transient transfection-fusion assay was established to investigate membrane fusion mediated by pseudorabies virus (PrV) glycoproteins. Plasmids expressing PrV glycoproteins under control of the immediate-early 1 promoter-enhancer of human cytomegalovirus were transfected into rabbit kidney cells, and the extent of cell fusion was quantitated 27 to 42 h after transfection. Cotransfection of plasmids encoding PrV glycoproteins B (gB), gD, gH, and gL resulted in formation of polykaryocytes, as has been shown for homologous proteins of **herpes simplex virus type 1 (HSV-1)**. However, in contrast to HSV-1, fusion was also observed when the gD-encoding plasmid was omitted, which indicates that PrV gB, gH, and gL are sufficient to mediate fusion. Fusogenic activity was enhanced when a carboxy-terminally truncated version of gB (gB-008) lacking the C-terminal 29 amino acids was used instead of wild-type gB. With gB-008, only gH was required in addition for fusion. A very rapid and extended fusion was observed after cotransfection of plasmids encoding gB-008 and gDH, a hybrid protein consisting of the N-terminal 271 amino acids of gD fused to the 590 C-terminal amino acids of gH. This protein has been shown to substitute for gH, gD, and gL function in the resp. viral mutants. Cotransfection of plasmids encoding PrV gC, gE, gI, gK, and UL20 with gB-008 and gDH had no effect on fusion. However, inclusion of a gM-expressing plasmid strongly reduced the extent of fusion. An inhibitory effect was also observed after inclusion of plasmids encoding gM homologs of equine herpesvirus 1 or infectious laryngotracheitis virus but only in conjunction with expression of the gM complex partner, the gN homolog. Inhibition by PrV gM was not limited to PrV glycoprotein-mediated fusion but also affected fusion induced by the F protein of bovine respiratory syncytial virus, indicating a general mechanism of fusion inhibition by gM.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMA

ACCESSION NUMBER: 2001:705925 CAPLUS
DOCUMENT NUMBER: 136:2706
TITLE: Varicella-zoster virus gB and gE coexpression, but not gB or gE alone, leads to abundant fusion and syncytium formation equivalent to those from gH and gL coexpression
AUTHOR(S): Maresova, Lucie; Pasieka, Tracy Jo; Grose, Charles
CORPORATE SOURCE: Departments of Microbiology and Pediatrics, University of Iowa, Iowa City, IA, USA
SOURCE: Journal of Virology (2001), 75(19), 9483-9492
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Varicella-zoster virus (VZV) is distinguished from **herpes simplex virus** type 1 (HSV-1) by the fact that cell-to-cell fusion and syncytium formation require only gH and gL within a transient-expression system. In the HSV system, 4 glycoproteins, namely, gH, gL, gB, and gD, are required to induce a similar fusogenic event. VZV lacks a gD homologous protein. In this report, the role of VZV gB as a fusogen was investigated and compared to the gH-gL complex. First of all, the VZV gH-gL experiment was repeated under a different set of conditions; namely, gH and gL were cloned into the same vaccinia virus (VV) genome. Surprisingly, the new expression system demonstrated that a recombinant VV-gH+gL construct was even more fusogenic than seen in the prior experiment with two individual expression plasmids containing gH and gL. Recombinant VV expressing VZV gB by itself, however, effected the formation of only small syncytia. When VZV gE and gB genes were cloned into one recombinant VV genome and another **fusion assay** was performed, extensive syncytium formation was observed. The degree of fusion with VZV gE-gB coexpression was comparable to that observed with VZV gH-gL: in both cases, >80% of the cells in a monolayer were fused. Thus, these studies established that VZV gE-gB coexpression greatly enhanced the fusogenic properties of gB. Control expts. documented that the **fusion assay** required a balance between the fusogenic potential of the VZV glycoproteins and the fusion-inhibitory effect of the

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ACCESSION NUMBER: 1990:604472 CAPLUS

DOCUMENT NUMBER: 113:204472

TITLE: Dextran sulfate inhibits the fusion of
influenza virus with model
membranes, and suppresses **influenza**
virus replication in vivo

AUTHOR(S): Luescher-Mattli, Madeleine; Glueck, Reinhard

CORPORATE SOURCE: Inst. Biochem., Univ. Bern, Bern, Switz.

SOURCE: Antiviral Research (1990), 14(1), 39-50

CODEN: ARSRDR; ISSN: 0166-3542

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effect of dextran sulfate and related compds. on the fusion of influenza A virus with model membranes, composed of dioleoylphosphatidylcholine and cholesterol (1:0.5), was investigated by a **fusion assay** based on dequenching of fluorescence of octadecylrhodamine-HCl (R18). Dextran sulfate samples of mol. weight of 500,000, 8000, and 5000 were found to be potent **inhibitors** of the virus-liposome fusion process. Polygalacturonic acid also showed antifusion activity, but to a lesser extent. Uncharged dextran, pos. charged diethylaminoethyl-dextran, and the monomer glucosamin-1,6-disulfate were ineffective. It was shown that dextran sulfate interacts with the virus. The results suggest that dextran sulfate binds to and inactivates the viral fusion protein.

ACCESSION NUMBER: 2001:211568 CAPLUS
 DOCUMENT NUMBER: 135:40500
 TITLE: The anti-**influenza virus** agent
 4-GU-DANA (Zanamivir) inhibits cell fusion mediated by
 human parainfluenza virus and **influenza**
virus HA
 AUTHOR(S): Greengard, Olga; Poltoratskaia, Natalia; Leikina,
 Evgenia; Zimmerberg, Joshua; Moscona, Anne
 CORPORATE SOURCE: Department of Pediatrics, Mount Sinai School of
 Medicine, New York, NY, 10029, USA
 SOURCE: Journal of Virology (2000), 74(23), 11108-11114
 CODEN: JOVIAM; ISSN: 0022-538X
 PUBLISHER: American Society for Microbiology
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB 4-GU-DANA (zanamivir) (as well as DANA and 4-AM-DANA) was found to inhibit the neuraminidase activity of human parainfluenza virus type 3 (HPF3). The viral neuraminidase activity is attributable to hemagglutinin-neuraminidase (HN), an envelope protein essential for viral attachment and for fusion mediated by the other envelope protein, F. While there is no evidence that HN's neuraminidase activity is essential for receptor binding and syncytium formation, we found that 4-GU-DANA prevented hemadsorption and fusion of persistently infected cells with uninfected cells. In plaque assays, 4-GU-DANA reduced the number (but not the area) of plaques if present only during the adsorption period and reduced plaque area (but not number) if added only after the 90-min adsorption period. 4-GU-DANA also reduced the area of plaques formed by a neuraminidase-deficient variant, confirming that its interference with cell-cell fusion is unrelated to inhibition of neuraminidase activity. The order-of-magnitude lower 50% inhibitory concns. of 4-GU-DANA (and also DANA and 4-AM-DANA) for plaque area reduction and for inhibition in the **fusion assay** than for reducing plaque number or blocking hemadsorption indicate the particular efficacy of these sialic acid analogs in interfering with cell-cell fusion. In cell lines expressing **influenza virus** hemagglutinin (HA) as the only viral protein, we found that 4-GU-DANA had no effect on hemadsorption but did inhibit HA2b-red blood cell fusion, as judged by both lipid mixing and content mixing. Thus, 4-GU-DANA can interfere with both **influenza virus**- and HPF3-mediated fusion. The results indicate that (i) in HPF3, 4-GU-DANA and its analogs have an affinity not only for the neuraminidase active site of HN but also for sites important for receptor binding and cell fusion and (ii) sialic acid-based **inhibitors** of **influenza virus** neuraminidase can also exert a direct, neg. effect on the fusogenic function of the other envelope protein, HA.

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